EUROGIN 2018 Abstracts

PART I - MAIN CONGRESS PROGRAM

MTC1. HPV induced cancers: rapid changes in epidemiology, carcinogenesis and natural history

00332

HPV induced cancers: rapid changes in epidemiology, carcinogenesis and natural history

02. Epidemiology and natural history

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Background / Objectives

HPV is the cause of almost all cervical cancer and is responsible for a substantial fraction of other anogenital cancers and oropharyngeal cancers. Understanding the HPV-attributable cancer burden can boost programs of HPV vaccination and HPV-based cervical screening.

Results

Attributable fractions (AFs) and the relative contributions of different HPV types were derived from published studies reporting on the prevalence of transforming HPV infection in cancer tissue. Maps of age-standardized incidence rates of HPV-attributable cancers by country from GLOBOCAN 2012 data are shown separately for the cervix, other anogenital tract and head and neck cancers. The relative contribution of HPV16/18 and HPV6/11/16/18/31/33/45/52/58 was also estimated.

Conclusion

Worldwide 4.5% of all cancers (630,000 new cancer cases per year) are attributable to HPV: 8.6% in women and 0.8% in men. AF in women ranges from <3% in Australia/New Zealand and the USA to >20% in India and sub-Saharan Africa. Cervix accounts for 83% of HPV-attributable cancer, two-thirds of which occur in less developed countries. Other HPV-attributable anogenital cancer includes 8,500 vulva; 12,000 vagina; 35,000 anus (half occurring in men) and 13,000 penis. In the head and neck, HPV-attributable cancers represent 38,000 cases of which 21,000 are oropharyngeal cancers occurring in more developed countries. The relative contributions of HPV16/18 and HPV6/11/16/18/31/33/45/52/58 are 73% and 90%, respectively.

References

Universal access to vaccination is the key to avoiding most cases of HPV-attributable cancer. As of January 2018, 79 countries (41%, mainly high-income high-income) have introduced the HPV vaccine. At the current pace of introductions, we are not on track to reach the 70% target by 2020. Given the above, on May 19th, 2018 the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, made a global call for action towards the elimination of cervical cancer. However, without a clear definition of cervical cancer elimination, whether that be disease eradication or prevalence of HPV viral infections, it will be difficult to effectively and efficiently accomplish this goal. This includes asking a) if we can reach cervical cancer elimination, b) what are potential vaccination, screening and treatment scenarios, c) how do we address strategies for special groups (e.g. HIV positive individuals), and d) what are the financial and economic resources required to reach the elimination targets.

References

de Martel , Plummer, Vignat and Franceschi: Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int. J. Cancer: 141, 664–670 (2017)

00595

Emerging issues on HPV transmission (genital, anal, oral)

02. Epidemiology and natural history

G. Dsouza

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Background / Objectives

This talk will review differences in HPV infection risk between men and women. Risk of genital HPV, anal HPV, and oral HPV will be discussed and compared between men and women. It has been noted that men have a higher incidence of oral HPV infection and HPV-related oropharyngeal cancer than women, data will be reviewed which will help to explain these differences between men and women.

Results

In session: MTC1. HPV induced cancers: rapid changes in epidemiology, carcinogenesis and natural history

References

NA

MTC2. Cervical cancer control: update on current practice

00433
Self-sampling

10. Self-sampling

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Background / Objectives

In several countries, HPV testing is being implemented as a primary method in cervical screening. HPV testing can be performed on self-collected (cervico-) vaginal material (HPV self-sampling), which makes it possible to offer self-sampling to women in cervical screening programs.

Results

In the Netherlands, a series of self-sampling studies have been performed among screening non-attendees (PROHTECT-1,-2,-3, and -3b), and a recent study among regular screening responders (IMPROVE).

Conclusion

PROHTECT studies have collectively shown that offering HPV self-sampling to non-attendees increases participation rates and is effective in detecting CIN3+/2+. Some countries now offer HPV self-sampling to this target group, including the Netherlands, and extension of this method to regular screening attendees can be envisioned. Importantly, prior to considering self-sampling for the regular screening population, clinical accuracy of HPV testing on self-collected as compared to clinician-collected samples needs to be established. Therefore, the IMPROVE-study, a randomised non-inferiority trial, was designed to evaluate the clinical accuracy of primary HPV testing on self-collected samples within an organized screening setting. Inclusion has been successfully accomplished and trial data are currently evaluated for performance of HPV testing on self-collected as compared to clinician-collected samples for detection of CIN3+/2+.

References

HPV self-sampling is a convenient and (cost-)effective method to overcome barriers to screening. When proven clinically non-inferior to HPV testing on physician-

collected cervical scrapes, HPV self-sampling may not only be used to complement current screening programs by increasing screening coverage (i.e., targeting non-attendees), but may also be offered as alternative to all women invited for cervical screening.

References

*) PROHTECT/IMPROVE study team: J Berkhof, FJ van Kemenade, LF Massuger, NJ Polman, VM Verhoef, AT Hesselink, DAM Heideman, RD Steenbergen, PJ Snijders, CJ Meijer, M Gök, L Rozendaal, R. Ebisch, RP Bosgraaf, RL Bekkers, WJ Melchers, J Bulten, LI Overbeek, AL de Vries, M Babović, JW Spruyt, F Voorhorst, JA Beliën, AC Molijn, W Quint; Departments of Pathology and Epidemiology/Biostatistics, Amsterdam UMC, Vrije Universiteit Amsterdam, Netherlands; Departments of Obstetrics/Gynaecology and Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; Department of Pathology, Erasmus MC University Medical Centre Rotterdam, Netherlands; DDL, Rijkswijk, Netherlands; PALGA, Houten, Netherlands; Screening Organisations Midden-West, Zuid-West and Oost, Netherlands; the National Institute for Public Health and the Environment (RIVM), Netherlands.

Remark SESSION MTC02 Sunday, December 2, 2018

MTC 02 Cervical cancer control: Update on current practice
Chair: Xavier Bosch

00430

Triage of HPV positive women

19. New technologies

K. Cuschieri [1], G. Ronco [2], A. Lorincz [3], L. Smith [4], G. Ogilvie [5], L. Mirabello [6], F. Carozzi [7], H. Cubie [8], N. Wentzensen [6], M. Arbyn [9], J. Monsonego [10], S. Franceschi [11]

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Background / Objectives

Molecular HPV testing is now the accepted modality for primary cervical screening. The requirement for optimal triage tests which can separate clinically significant from benign HPV infection is thus extremely timely.

Results

The EUROGIN 2017 roadmap (1) set out to summarise the evidence in support of the most applied triages; cytology (with or without adjunctive p16/Ki67), limited genotyping and methylation markers. In addition, the challenges of implementing triage strategies including the increased use of self sampling, provision for low and middle income countries (LMIC) and the impact of vaccination were considered as were communications to support effective implementation. Key themes from this roadmap will be presented as will more recent technology updates related to triage.

Conclusion

Cytology is the triage strategy associated with the most data on performance although the HR-HPV positive, cytology negative group presents challenges and re-testing intervals for this group (and choice of re-test) require careful consideration. As cytology relies on subjective skills, p16/Ki67 can mitigate disparities, although a clinician-taken sample is still required. Comparatively, genotyping and methylation markers are objective and applicable to self-taken samples, offering logistical advantages including in LMIC. However, limited typing

may have diminishing returns in immunised populations. While viral and cellular methylation markers show promise, more prospective data are needed.

References

Systems that can detect multiple cellular and viral targets concurrently such as next generation sequencing platforms will inform the development of triage tools. Furthermore, a multi-step approach to triage may be advantageous provided this does not create complex pathways. Inevitably, the balance of risk to cost(s) will be key in decision making. Defining an acceptable level of risk will help inform such decisions, although this will likely differ between settings. Finally, given the variety of triage options currently offered for triage, appropriate education of both health care providers and the public is essential to ensure informed and high engagement.

References

Cuschieri K, Ronco G, Lorincz A, Smith L, Ogilvie G, Mirabello L, Carozzi F, Cubie H, Wentzensen N, Snijders P, Arbyn M, Monsonego J, Franceschi S. Eurogin roadmap 2017: Triage strategies for the management of HPV-positive women in cervical screening programs. Int J Cancer. 2018 Aug 15;143(4):735-745. doi: 10.1002/ijc.31261. Epub 2018 Feb 8. Review. PubMed PMID: 29341110.

MTC3. Non-cervical HPV-related cancers: the key issues

00569

Penile pre-cancers and cancers

03. Pathogenesis

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Background / Objectives

To review the clinical presentation, histopathology, HPV status and management of penile pre-cancers and cancers

Results

Literature review

Conclusion

There is a spectrum of clinical presentations of penile pre-cancers and cancers. High grade pre-cancer is strongly HPV- associated (80-90%) whereas reported HPV prevalence in invasive cancers ranges from 33-66%. Histopathologic subtypes are well described showing greater (warty/basaloid) and lesser (keratinizing) association with HPV. Treatment is usually surgical, and a subset of invasive cancers can now be treated with penile sparing techniques.

References

Penile cancer remains a rare but morbid condition, and early diagnosis is central to improved outcomes.

References

Fernandez-Nestoza MJ, *et al*. Human papillomavirus genotypes in condylomas, intraepithelial neoplasia, and invasive carcinoma of the penis using laser capture microdissection (LCM)-PCR. Am J Surg Pathol 2017;41:820-32

00182
Vulvar pre-cancers and cancers

24. Vulvar diseases and neoplasia

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Background / Objectives

Although both vulvar and cervical neoplasia have similar presentation, the vulva is different than the cervix as it does not contain a squamous columnar junction, and it includes keratinized skin, which may develop dermatological diseases. This difference between the vulva and cervix affects the difference between the neoplasia development, diagnosis and treatment. Several **key issues** currently deserve further study:

Results

Epidemiology: There is an unexplained difference between geographic areas in the incidence of precancers and cancer of the vulva. In addition, the incidence of high grade vulvar squamous intraepithelial Lesion (VHGSIL, formerly - VIN 3), and of squamous vulvar cancer continue to increase.

Etiology: While with cervical cancer, almost all precancers and cancers are caused by HPV, in vulvar precancers and cancer there is a dual etiology: HPV causes most neoplasms, and the rest are associated with chronic vulvar dermatoses, mainly Lichen Sclerosus, via a yet undefined mechanism.

Terminology: In 2015, International Society for the Study of Vulvovaginal Disease (ISSVD) published a classification system, similar to the 2014 World Health Organization (WHO) terminology. The new terminology was formulated as a result of concerns raised with the LAST terminology. The 2015 ISSVD terminology includes:
●Low-grade squamous intraepithelial lesion (LSIL) of the vulva
●High-grade squamous intraepithelial lesion (HSIL) of the vulva
●VIN differentiated type (dVIN)

Conclusion

Screening and diagnosis: Screening is not currently recommended. Diagnosis delays due to patient and health care provider's delays are still frequent. Occult carcinoma may be missed in women with vulvar lesions.

Treatment: Treatment may be mutilating with physical and psychosocial sequela. Tailoring treatment is required, according to localization, histopathology and size of the lesion. Medical treatment for precancers is still explored.

Vaccination: While prophylactic vaccination has shown to be successful, therapeutic vaccines are still in study.

References

Various aspects of vulvar precancers and cancers need further research.

MTC4. HPV research priorities: new and future directions

00552

Molecular characterization of HPV16 sub-lineages: viral sequences, integration events, and human somatic mutation landscape

01. Viral and molecular biology

M. Dean [1], H. Lou [2], J. Boland [2], E. Torres Gonzalez [1], A. Albanez [3], W. Zhou [2], M. Steinberg [2], L. Diaw [1], D. Roberson [2], M. Cullen [2], L. Garland [2], F. Castillo Pinto [3], S. Bass [2], R. Burk [4], M. Yeager [2], N. Wentzensen [5], M. Schiffman [5], L. Mirabello [5], E. Gharzouzi [3]

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Background / Objectives

Cervical cancer is the most frequent cause of cancer mortality for women living in poverty and is almost exclusively caused by the human papillomavirus (HPV). To better understand the molecular characteristics of HPV and the cervical tumor genome we have surveyed 665 cases of cervical cancer from Guatemala.

Results

Tumor DNA was sequenced by the capture of the exons of 245cancer-related genes, and variants called, and somatic mutation filtered. HPV 16 DNA was sequenced using a previously validated panel of overlapping primers, aligned to the viral genome and sub-lineage determined by phylogenetic analysis.

Conclusion

The average age is 52 and the number of children is 6.0, 5.6% report tobacco use; 56% have stage 2 or 3 cancer and 82% of tumors are squamous cell carcinoma. In total, 20% of subjects report a family history of any cancer and 6% for cervical cancer. Patients with a family history of cervical cancer have a younger age of onset

(47 years) and were pre-menopausal cancer (57% versus 42% in the entire sample). In total, 11/24 tumors have a mutation in the *PIK3CA* gene (46%) and 58% of tumors have at least one mutation in the PI3K pathway. Other known driver mutations include *TP53*, *RB1*, and *CASP8*. Mutations in chromatin remodeling genes (*PBRM1*, *EP300*, *SMARCA4*, *KMT2C*, *KMT2D*, *HIST1H3B*, *HIST1H4E*, *HIST1H1E*) are also elevated with 46% of tumors having at least one mutation. Tumors have an average of 18 mutations (median 14); however, 4 tumors have high (32-38 mutations) or very high (63-64) mutation load. All hypermutation subjects have *PIK3CA* mutations and are post-menopausal. Mutation signature analysis shows that the highest signature is for APOBEC-related mutations (46%) and HPV is known to activate APOBEC. Pre-menopausal patients have a lower mutation load (mean 13 mutations) and a lower fraction of APOBEC-related mutations (40%). Overall HPV16 accounts for 58% of HPV infections in Guatemala. We have sequenced and variant classified 96 HPV16+ cervical cancers and found that the D2 and D3 sub-lineages represented 26% and 29% of the samples, respectively. A total of 65% (62/96) of the samples had integrated HPV16 sequences as determined by HPV DNA capture and sequencing, and A1 and D2 sub-lineages showed a higher frequency of integration 78-79%) compared to D3 (44%). Subjects with HPV16 integration have a significantly younger age (P=0.009), and D2 was observed in younger patients, as compared to A1 (P=0.001).

References

Guatemalan cervical tumors have a similar profile of somatic mutations to those in the US, with a high frequency of *PIK3CA* mutations, and the very high-risk HPV16 D2, D3 sub-lineages.

References

Lou H, Villagran G, Boland JF, et al. Genome Analysis of Latin American Cervical Cancer: Frequent Activation of the PIK3CA Pathway. Clin Cancer Res 2015;21:5360-70.

Mirabello L, Yeager M, Cullen M, Boland JF, Chen Z, Wentzensen N, Zhang X, Yu K, Yang Q, Mitchell J, Roberson D, Bass S, Xiao Y, Burdett L, Raine-Bennett T, Lorey T, Castle PE, Burk RD, Schiffman M. HPV16 Sublineage Associations With Histology-Specific Cancer Risk Using HPV Whole-Genome Sequences in 3200 Women. J Natl Cancer Inst. 108: 2016.

Cullen, M., Boland, JF, Schiffman, M., et al. Deep sequencing of HPV16 genomes: A new high-throughput tool for exploring the carcinogenicity and natural history of HPV16 infection. Papillomavirus Res. 2015; 1: 3– 11.

00556

3D Squamous Epithelial Tissue Culture System for Anti-HPV Drug Discovery and Validation

01. Viral and molecular biology

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Background / Objectives

Management of HPV lesions requires better therapeutic options than are presently available. We established a three-dimensional epithelial tissue culture system from primary human keratinocytes harboring HPV-18 replicons, fully recapitulating a robust infectious program (Wang et al. 2009). Systematic investigations of virus-host cell interactions in such 'raft' cultures grown at the liquid medium/air interface (Dollard et al. 1992; Wilson et al. 1992) have identified critical regulatory pathways on which HPV DNA amplification depends, revealing potential host targets for anti-viral therapies. Our strategy is to repurpose existing pharmacologic agents to inhibit viral DNA amplification, interrupt HPV transmission, or preferentially eradicate HPV-infected cells.

Results

Inhibitors are delivered to HPV-18 infected as well as to uninfected control PHK raft cultures either topically or through the tissue culture medium for up to two weeks before harvesting the tissues. In addition, durability of responses is evaluated after a post- exposure chase period. We then probe FFPE tissue sections for HPV DNA amplification, cellular DNA replication, papillomaviral proteins E6, E7 and L1, targeted host proteins, and tissue morphology, as well as for markers of DNA damage and apoptosis. Duplicate rafts are used for HPV DNA copy number evaluation to ascertain that there is a wide dynamic range between unimpeded viral DNA amplification and inhibited infections, typically 100-fold or more. Additional cultures can be used to evaluate specific mRNAs and micro-RNAs. Rafts can also be established from HPV-immortalized or -transformed epithelial cells or cervical cancer cell lines. Moreover, 3D cultures can be grown directly from patient lesions.

Conclusion

Based upon host cell metabolic and regulatory pathways essential for maintenance of the viral genome, replicative amplification and virion morphogenesis, we are systematically investigating inhibitors of mitogen-activated protein kinases, histone deacetylases, DNA Damage Responses including cell cycle checkpoints (Banerjee et al, 2011), replicative DNA amplification, and cytoplasmic vesicle function as well as inducers of stress responses. Using the 3D raft culture system, we have identified molecularly distinct inhibitor candidates as safe and effective. Several such agents are advancing to clinical trials to treat benign HPV lesions (Banerjee et al., 2018).

References

These proof-of-principle experiments demonstrate the potential for discovery of new drugs against epitheliotropic viruses. The authenticity of 3D experimental models of HPV infections and diseases should greatly reduce preclinical research time and expense.

References

Dollard et al., 1992. Genes & Development 6: 1131-1142. PMID: 8382318.

Wilson et al. 1992. Cell Growth and Differentiation 3: 471-483. PMID: 1390334.

Wang et al. 2009. Genes & Development 23: 181-194. PMID: 19131434.

Banerjee et al. 2011. J. Biol. Chem. 286: 15473-15482. PMID: 21321122.

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00630

Is HPV-negative cervical cancer a biologically different entity?

02. Epidemiology and natural history

J. Lei [1], K.M. Elfström [2], A. Ploner [1], C. Lagheden [3], C. Eklund [3], S. Nordkvist Kleppe [3], B. Andrae [4], J. Dillner [5], P. Sparén [1], K. Sundström [5]

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Background / Objectives

High risk human papillomavirus (hrHPV) infection is established as the major cause of invasive cervical cancer (ICC). Yet there seems to be a subset of cervical cancers where hrHPV is not readily detectable in the tumor tissue by standard PCR methods.

Methods

We recently described findings from an analysis of national registers and comprehensive HPV genotyping of all cervical cancer cases diagnosed in Sweden during the years 2002-2011.

Results

Of the 2845 included cases, hrHPV was detected in 2293 cases (80.6%) using general primer PCR with Luminex genotyping and real-time PCR targeting the E6/E7 regions of HPV16/18. Women with hrHPV-positive cervical tumors had a substantially better prognosis than women with hrHPV-negative tumors, independently of already established clinically relevant factors.

Conclusion

This raises the question whether L1 negative tumors are biologically different from L1 positive tumors. In this presentation, we will discuss different definitions of hrHPV

negativity, sensitivity of laboratory detection methods, and resulting implications for research and practice.

00230

SAFETY AND EFFICACY OF PROPHYLACTIC HPV VACCINES. A COCHRANE REVIEW OF RANDOMISED TRIALS

09. HPV screening

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Background / Objectives

Recently, the evidence on efficacy and safety of prophylactic HPV vaccines derived from randomised controlled trials (RCTs) was published in the Cochrane database of Systematic reviews. A summary of this Cochrane review is presented below.

Results

Only RCTs involving mono-, bi- and quadri-valent HPV vaccines were included. Trials evaluating the nona-valent vaccine were excluded since women in the control group received the quadri-valent vaccine. Main outcomes were: histologically confirmed cervical precancer lesions distinguishing those associated with vaccine HPV types and any cervical precancer. Exposure groups were: young women (15-26 years) or mid-adult women (24-45 years) being initially negative for high-risk HPV (hrHPV) or negative for HPV types included in the vaccine and women unselected by HPV status.

Conclusion

All evaluated vaccines offered excellent protection against cervical intra-epithelial neoplasia of grade 2 or 3 (CIN2/CIN3) and adenocarcinoma-in-situ (AIS) associated with HPV16/18 infection in young women who were not initially infected with hrHPV or HPV16/18. Vaccine efficacy decreased when women regardless of HPV DNA status at enrolment were included. Vaccine protected also in young women but at a lesser degree against any cervical precancer. Vaccine efficacy was lower in mid-adult women. Trials were not empowered to address protection against cervical cancer. Occurrence of severe adverse events or adverse pregnancy outcomes was not significantly higher in recipients of HPV vaccines than in women included in the control arms.

References

To complete evidence from randomised trials, careful population-wide surveillance of HPV vaccine effectiveness (targeting also incidence of HPV-related cancers) and safety (including also rare conditions such as neurologic and auto-immune syndromes) should be set up by linking vaccination, cervical cancer screening and morbidity registries.

References

KEYWORDS: Cervical cancer, HPV vaccines, safety, randomised clinical trials, systematic review, meta-analysis.

00075

RNA SEQUENCING OF HUMAN PAPILLOMAVIRUS NEGATIVE INVASIVE CERVICAL CANCERS

11. Genotyping

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Background / Objectives

Although cervical cancer is known to be caused by human papillomavirus (HPV), some tumors appear to be HPV-negative by primer-based detection systems.

In a previous study, we identified and requested FFPE blocks from all cervical cancers in Sweden during 2002 to 2011 (n=4254). Out of the 2850 cancer cases with adequate HPV typing results, there were 394/2850 (13,8%) cases being “apparently HPV-negative” after being tested for HPV DNA with both PCR with MGP primers targeting L1 gene and real-time PCR with primers targeting the E7 gene. We wish to perform unbiased testing (not based on PCR or other methods requiring prior knowledge of sequences) to see which actively transcribed viruses could be found in “apparently HPV-negative” cancer cases.

Results

As a pilot study, we included six cervical specimens “apparently negative” for HPV. Cervical specimens were RNA extracted with a xylene-free method, rRNA depleted, reverse transcribed and ligated to individual adapters using the TruSeq Stranded Total RNA kit (Illumina, US). Libraries were validated, normalized to 2 nM and pooled before sequencing. Sequencing was performed in the NextSeq500 system (Illumina, US) at 151 paired-end cycles. 150 bp long quality reads were screened against the human reference genome hg19 and human reads were filtered from the data set. Fastq files for each sample, were aligned to all HPV types reference clones sequences published in the website of the International Human Papillomavirus Center (hpvcenter.se, accessed 2018-05-28).

Conclusion

3/6 samples were positive for HPV RNA, with HPV 213 (Gamma-13), HPV 197 (Gamma-24) and HPV type 16 (Alpha-9) being found in one specimen each. While HPV 197 had 3524 reads covering all HPV genes (E6, E7, E4, E2, E1, L2 and L1), the HPV 213 and HPV 16-positive specimens showed reads only mapping to their respective E1 genes.

References

In Illumina total RNA sequencing data with a median of 30 million reads per sample, HPV transcription was detected in 3/6 apparently “HPV-negative” cervical cancer specimens (negative in PCRs directed to the L1 and E7 regions). The HPV197 and HPV213 may have escaped detection due to mismatch to primers/probes in the conventional PCR-based HPV detection systems.

00202

Nine years of the SCOTTISH HPV ARCHIVE - A resource support for basic and applied HPV research

19. New technologies

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Background / Objectives

Biobanking is essential to support HPV-associated basic and clinical research. A recent survey of key opinion leaders confirmed this as a top 10 priority for HPV based research and development. Some of the key considerations for biobanking are: to ensure samples are stored and disseminated with due process of governance; ensuring samples are of the nature and quality to support contemporary, priority research; and sustainability models.

Results

The Scottish HPV Archive received government core-funding for the first five years and then has been sustained via research funding and a revenue model based on sample provision. Several permissions were sought to ensure robust and informative linkage to relevant clinical information and recently the archive was added within the Lothian NRS BioResource[1]. Access to samples is obtained through application to a multi-disciplinary archive steering committee[2].

As a dynamic archive, it is a collection of collections and includes samples from women attending routine screening in addition to research collections associated with specific inclusion criteria. Currently, the archive contains over 45,000 samples (37,613 liquid based cytology, 8,231 nucleic acid extracts and 863 self-taken vaginal swabs). Samples are annotated with HPV and vaccination status, as well as pathology information. Quality assessment is performed regularly to assess best storage conditions for viable cells, DNA, RNA and protein.

Conclusion

To date, 51 applications have been approved for use, with an increase in applications over the last two years. Requests are associated with research into HPV epidemiology (5, 9.8%), new technologies for HPV detection (20, 39.2%), validation and assessment of HPV detection assays (17, 33.3%) and basic research into HPV (9, 17.6%). The applications have been both from United Kingdom (40, 78.4%) and international partners (11, 21.6%%); and 11 (21.6%) have involved commercial collaborations. The archive has been associated with several grants and peer reviewed publications[3] with outputs disseminated at national and international microbiology and oncology meetings. A recent challenge is the increasing and understandable demand that is made on nucleic acid quality and yield (from clinical samples) to reconcile with sophisticated molecular technologies that require long reads. Our intention is to maximise/optimise processing extraction and storage conditions to enhance quality.

References

In the nine years since its establishment, the Scottish HPV Archive has proved to be a valuable resource for researchers. Our aim is to further collaborate with the international community to: establish best practice for biobanking, determine what type of samples would support research optimally and consider joined-up options for funding/sustainability.

References

[1]www.nhsresearchscotland.org.uk/research-in-scotland/facilities/biorepositories-and-tissue-services

[2]hpvarchive@ed.ac.uk

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00091

A Danish Clinical Cervical Cytology Biobank. Pilot studies of sample processing and quality

20. Diagnostic procedures / management

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Background / Objectives

Using liquid-based cytology usually only a smaller portion of the collected material is used for primary diagnostics (cytology and/or HPV testing.) The residual material is stored in either uncontrolled condition or discarded. For the purpose of future diagnostics and in order to continuously monitor and evaluate new screening methods and biomarkers, a cervical cytology biobank is very valuable. The objective of this study was to identify and evaluate an efficient workflow for establishing a cervical cytology biobank with high cell yield and high quality of the stored material.

Results

The biobank will consist of residual material from liquid-based cytology samples (ThinPrep, Hologic) collected from women participating in the national screening program for cervical cancer in the uptake area of Sygehus Lillebaelt, Denmark (approx. 50,000 samples/year).

The workflow shown in figure 1 is automated using the Freedom Evo 200 robot (Tecan), and information on samples and storage is administrated by the Labware LIMS system.

Cell yield was evaluated by measuring the amount of DNA in the original ThinPrep vial compared to the yield of DNA in the biobanked sample.

As an estimate of quality biobanked samples were examined by PCR with a 600 bp amplicon and with an NGS panel (TST15 panel, Illumina). In addition, imprint of a subset of samples have been compared before and after biobanking.

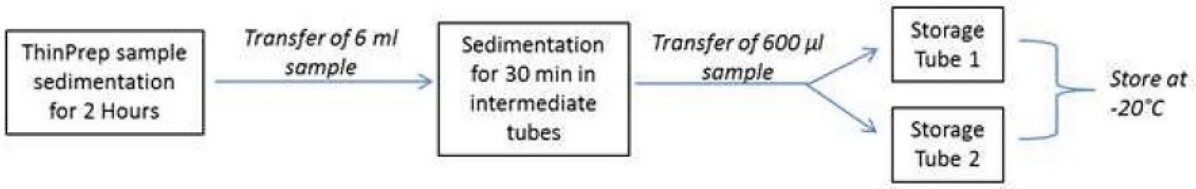
Conclusion

Based on 24 samples the DNA yield in storage tube 1+2 was on average 47% of the content in the primary tube. PCR results showed that 600 bp amplicons could be amplified for all samples, revealing high quality DNA. The DNA is also useful for NGS, as the analysis using the TST15 panel showed good quality parameters and high amplicon coverage.

A gynecological pathologist examined the imprint from samples before and after biobanking and no differences were observed, indicating that cells in the biobank are intact and could be used for analyses like IHC, FISH etc.

References

Using the presented workflow, a cytology biobank has just been initiated. Updated and further data on quality measurements of DNA, RNA and protein will be presented. The biobank holds great potential for future clinical purposes as wells as for research and quality assurance.



MSS1. HPV vaccine efficacy and perspectives

00473

Decreasing Cervical Cancer Trends Among Females Aged Younger than 40 Years — United States, 1999–2014

02. Epidemiology and natural history

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Background / Objectives

Human papillomavirus (HPV) vaccination and cervical cancer screening can prevent cervical cancer. Recent cervical cancer trends among females aged <40 years (approximately 25% of all cases) can help characterize the landscape of cervical cancer following changes to both vaccination and screening. In 2006, the HPV vaccine was introduced and from 2009-2012 12, there were several revised screening recommendations to prevent overdiagnosis and harms among females at low risk for cervical cancer, including less frequent screening and later-age initiation.

Results

Using US Cancer Statistics covering 97% of the US population (1999–2014), we calculated invasive cervical cancer incidence rates among females aged 15–39 years. Rates were standardized to the 2000 US standard population. Rates were not calculated if there were <16 cases. Differences in trends were examined using parallelism comparability testing. In addition, the discussion will include modeling, typing, and age-period cohort analyses.

Conclusion

During 1999–2014, 3,188 cervical cancer cases occurred annually among US females aged 15–39 years. Incidence rates increased with age (0.2 per 100,000 for 15–19 years to 14.0 per 100,000 for 35–39 years). Rates decreased significantly from 1999 to 2014 among ages 20–24 years (annual percentage change (APC) = -3.6% per year), 25–29 years (APC=-2.7%), 30–34 years (APC=-1.9%), and 35–39 years (APC=-1.2%). Among ages 15–19 years, rates decreased during 1999–2009, but overall trends were not calculated because of small counts during 2010–2014. Trends differed between ages 15–34 years and 35–39 years (P <.05).

References

Cervical cancer incidence rates decreased during 1999–2014 among females aged 15–39 years, with larger declines among younger age groups. These decreases are reassuring given recent changes in screening recommendations for later and less frequent screening. HPV vaccination has been shown to reduce infection and precancers; longer-term surveillance will be needed to monitor corresponding reductions in cervical cancer. Timely, appropriate screening and continued HPV vaccination may result in further declines in cervical cancer

00325

Cervical cancer rates in Australia: predicting the declines due to vaccination and screening policy

05. HPV prophylactic vaccines

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Background / Objectives

Australia was one of the first countries to introduce a national HPV vaccination program in 2007, and has achieved high coverage in females, and more recently in males. Australia has now also transitioned from 2-yearly cytology-based screening to 5-yearly primary HPV screening for women aged 25-74. We predicted the combined impact of these policy changes and aimed to identify the earliest years by which cervical cancer incidence rates in Australia (currently ~7/100,000) would drop below the rare cancer threshold (6/100,000) and a lower threshold (4/100,000), as it is likely to be one of the first countries globally to reach these benchmarks.

Results

We utilised Policy1-Cervix, an extensively validated dynamic model of HPV vaccination, natural history, and cervical screening to estimate cervical cancer incidence to the end of the century. We modelled detailed vaccination coverage rates including the initial catch-up program, inclusion of boys from 2013, and the change to the nonavalent vaccine ('HPV9') from 2018 onwards. We also captured the transition to the 5-yearly primary HPV screening program. Screening recommendations for cohorts offered HPV9 are as yet unknown so we considered two recommendation scenarios for these HPV9 cohorts: (1) no screening and (ii) 5-yearly primary HPV testing.

Conclusion

Cervical cancer incidence is predicted to drop below the rare cancer threshold by 2020 and to drop below 4/100,000 by 2028, regardless of screening assumptions for HPV9 cohorts. Incidence will drop below 1/100,000 by 2067 if screening continues for cohorts offered HPV9, or below 3/100,000 by the end of the century, if HPV9 cohorts are not screened.

References

If high-coverage vaccination and screening is maintained, cervical cancer incidence could drop below 4/100,000 in Australia before 2030. Cervical cancer incidence rates are expected to be very low by the end of the century, but the absolute level will vary depending on screening recommendations for HPV9 cohorts.

00570

Predicting declines in cervical cancer due to vaccination: the global perspective

36. Public health

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Background / Objectives

Cervical screening and human papillomavirus (HPV) vaccination have been implemented in most high-income countries; however, coverage is much lower in low-and-middle-income countries (LMIC). Recently, the Director-General of the World Health Organisation announced a call-to-action for the elimination of cervical cancer as a public health problem. An elimination threshold in terms of cervical cancer incidence has not yet been defined, but an absolute rate of cervical cancer incidence could be chosen for such a threshold. We aimed to (i) quantify the impact of increased global vaccination and screening coverage on cervical cancer cases over 2020-2069, and (ii) extend predictions out to 2099 to identify the earliest years by which cancer incidence could drop below the rare cancer threshold (6 per 100,000) and a potential 'elimination' threshold (4 per 100,000).

Results

We performed a statistical analysis of trends combined with a dynamic multi-cohort model of HPV vaccination and cervical screening ('Policy1-Cervix') to evaluate the impact of potential future prevention scenarios.

Conclusion

In the absence of further intervention, over the period 2020-2069, 44.4M cervical cancer cases are predicted to occur, with almost two-thirds occurring in low or medium HDI countries. Rapid vaccination scale-up could avert 6.7-7.7M cases in the period, but more than half of these will be averted after 2060. Implementing twice-lifetime HPV-based screening in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert an additional 5.7-5.8M cases in the next fifty years. Rapid scale-up of combined high-coverage screening and vaccination from 2020 onwards will result in average cervical cancer rates for very-high, high, medium and low HDI countries declining to <6 per 100,000 by 2045-2049, 2055-2059, 2065-2069 and 2085-2089, and to <4 per 100,000 by 2055-2059, 2065-2069,

2070-2079 and 2090-2100, respectively. However, rates of cervical cancer will remain above 4 per 100,000 in many high burden African countries.

References

Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has potential to avert up to 13.5M cases by 2069 and could achieve average cervical cancer incidence rates of <4 per 100,000 globally, and in all HDI categories, by the end of the century.

MSS3. Triage markers for HPV-positive women: long term performance

00358

TRIAGE MARKERS FOR HPV-POSITIVE WOMEN: p16 VS p16/Ki67

12. Molecular markers

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Background / Objectives

The accumulation of cyclin-dependent kinase inhibitor 2A (p16ink4a) protein in a cell is associated with neoplastic progression in precancerous cervical lesions. p16/Ki67 dual staining has been proposed as a triage test in cervical cancer screening for HPV-positive women. In 2008, within NTCC trial (New Technologies for Cervical Cancer), p16 immunostaining was used as triage test and cross-sectional and longitudinal results were published. Evidences from large prospective studies were published too, comparing p16/Ki67, cytology and HPV testing as triage markers.

Results

In NTCC, women aged 25-60 were enrolled in a randomised multicentre trial comparing primary HPV testing and cytology; p16 was tested by immunostaining in 1042 HPV positive women. Sub-studies nested into large population trials (KPC, Athena trial, PALMS) enrolled HPV-positive women to test triage with p16/Ki67 against cytology or HPV test. A study from Umbria (Italy) selected 396 HPV-positive women from local screening program: p16/Ki-67 and E6/E7 mRNA were used as triage markers. In 2014, 2651 HPV positive women were enrolled in a new randomized trial (NTCC2, 38535 women), to compare p16/Ki67 and cytology as triage tests.

Conclusion

In NTCC, 31 CIN2+ of 365 p16-positive women (8.8%) and 17 CIN2+ of 579 p16-negative (3.7%) women were detected, with a relative risk (RR) of 2.61; 16 and 6 CIN3+ were detected in the same populations respectively (4.4% vs 1.3%); RR was 3.90. Longitudinal sensitivity of p16 for CIN3+ detection was 77.8% (all ages). The relative sensitivity using conventional cytology was 2.08 (35-60y) and 2.86 (25-34y). Cumulative risk for CIN3+ was 2.0% for HPV-positive/p16-negative women, 0.01% for HPV-negative women and 0.04% for cytologically normal at recruitment. In KPC

study, the risk of pre-cancer in p16/Ki-67-positive and negative women was 12.4% and 1.6% respectively. p16/Ki67 sensitivity was 74.9% vs 51.9% for cytology in Athena study. p16/Ki67 have shown a sensitivity for CIN2+ of 94.4% vs 100% for HPV test in ASC-US cases and 85.7% for LSIL (PALMS). Sensitivity was 87.6% (ASC-US) and 80.8% (HSIL) for p16/Ki-67 vs 77.6% and 53.2% for cytology in Umbria's trial.

References

The p16/Ki67 dual-staining has been introduced to decrease the need for morphologic evaluation of p16 stained cells and to reduce the subjectivity of the evaluation. The reproducibility of dual-staining interpretation is good to excellent confirming its robustness as a triage test of HPV-positive women. Multicenter trials have confirmed these findings and have shown a good risk stratification for HPV-positive women, proving p16/Ki67 dual-staining usefulness in reducing the number of unnecessary colposcopy referrals.

References

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00434

Triage using self-taken samples.

12. Molecular markers

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Background / Objectives

Offering self-sampling of (cervico-)vaginal material for high-risk HPV testing is an effective method to increase screening coverage. However, an additional triage test is necessary to identify HPV-positive women with clinically meaningful disease. Cytology triage cannot be reliably performed on self-sampled material; asking for alternative triage markers that can be directly applied to this sample type. Candidate molecular triage markers involve HPV16/18 genotyping or aberrations in host cell genes that underlie progression to cancer, such as DNA hypermethylation.

Results

In various studies, the performance of HPV16/18 genotyping and a series of candidate methylation target genes was evaluated on both lavage- and brush-based self-samples of HPV-positive women.

Conclusion

The performance of HPV16/18 genotyping on HPV-positive self-samples revealed an accuracy which appeared to be comparable to that on HPV-positive cervical scrapes (CIN3+ sensitivity 65.4-69.4%, specificity 65.0-70.9%). Also methylation levels between sample types were significantly correlated, with strongest correlation in women with CIN3+ (Spearman's ρ 0.697, P<0.001). Methylation analysis, including markers FAM19A4, mir124-2, ASCL1, LHX8 or ST6GALNAC5, demonstrated a good clinical performance for CIN3 detection in both lavage and brush self-sample, with sensitivity up to 74-88%; and specificity up to 79-81%. Importantly, all self-samples from women with cervical cancer scored DNA methylation-positive. Recent longitudinal outcome data of methylation analysis on HPV-positive cervical scrapes from a screening cohort illustrate a low 14-year cervical cancer risk among baseline methylation-negative women as compared to baseline cytology–negative women (risk difference: 0.71% [95% CI: 0.16-1.4]).

References

Host cell DNA methylation analysis, possibly in combination with HPV16/18 genotyping, serves as an attractive molecular triage marker for HPV-positive women, with the advantage of applicability to self-collected samples. Our findings indicate that a transition towards full molecular self-screening in HPV-based cervical screening programs is feasible.

References

Remark: Session Monday, December 3, 2018 2:15 PM - 3:45 PM, Auditorium I
MSS Triage markers for HPV-positive women: long term performance
Chair: Marc ARBYN, Kate CUSCHIERI

00589

E6-E7 ONKOPROTEIN EXPRESSION AS TRIAGE MARKERS FOR HPV POSITIVELY SCREENED WOMEN

20. Diagnostic procedures / management

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Background / Objectives

The Human Papillomavirus life cycle is dependent on coordinate expression of the viral structural late and the regulating early expressed genes. In particular, the interference with cellular proliferation and differentiation by E7 and the abrogation of apoptosis by E6, in conjunction with additional pleiotropic effects of both viral proteins, are hallmarks of virally induced alterations of cellular fate. Both effects are first steps in prolonged cellular survival necessary for virus production and cellular transformation as well as progression to invasive cancinoma. While in HPV early infection the oncoprotein expression is low and tightly regulated, in higher grade lesions the expression is markedly increased. This is due to more cells being present harboring HPV in larger more advanced dysplastic tissue areas but also in an enhanced expression per cell. This upregulation can be detected by innovative assays.

Firstly, mRNA coding for E6 and/or E7 can be quantified and related to cellularity giving a measure for the strength of transcriptional overexpression. Secondly, the oncoproteins themselves can be detected by immuno assays due to the development of antibodies with sufficient affinity und sensitivity directed specifically to the E6 or E7 protein of specific HPV genotypes. Two formats are available using lateral flow and ELISA platforms to detect E6 and E7 expression, respectively. Initial studies using such assays show a potential for triage of HPV positive women to colposcopy.

Results

(Invited talk for plenary session: Triage markers for HPV-positive women: long term performance)

MSS4. From cytology to HPV based screening

00302

From cytology to HPV based screening - Part A: Europe : operational experiences from transforming screening programs: lessons learned: Italy

09. HPV screening

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Background / Objectives

The Italian National Prevention Plan 2014-2018 established among the aims for the Regional Health Systems the complete transformation of the cervical cancer screening from Pap to HPV-based by the end of 2018. The protocol for implementing HPV-based screening has been established in 2012 with the Italian contextualization of the European guidelines: Pap every 3yy until the age of 30/35, then HPV every 5yy up to 64. HPV-positive women undergo cytology triage, if ASC-US or more severe they are referred to colposcopy, if negative they are referred to 1 year HPV retesting; at retesting women still HPV-positive are referred to colposcopy.

Results

Data from the National Screening Monitoring Centre (women invited in 2015 and 2014)(1) and fron the National Health Interview are presented (2013-2016) (2)

Conclusion

In the period 2014-2017 79% of the women aged 25-64 declared to be up-to-date with cervical cancer screening (a Pap in the last 3yy or an HPV test in the last 5yy), 45% within the organized screening programmes and 34% with opportunistic testing. Very few is known about opportunistic testing, but it is mostly based on Pap-test and in minority on co-testing.

In 2016, 22.9% of the target population has been invited for HPV test by the screening programs, with large differences between geographic areas (33% in North, 25% in Centre and 9% in south). The proportion is increasing, being 8% in 2012 and 13% in 2014, but it is far from the target proposed by the Italian MoH.

HPV positivity is 7.0%, among HPV positive 34% are cytology positive and referred to colposcopy. Compliance to 1 year repeat is about 75%, with large differences between centres. HPV clearance at 1 year is about 50%. The overall colposcopy referral is 3.6%, CIN2+ detection rate is 5.4/1000 screened women, and positive predictive value (PPV) was 14.8%; in the same period cytology screening had 2.6% colposcopy referral, 3.8/1000 detection rate and 16.7% PPV.

For some screening programs, data from women who had been previously screened with HPV are available. HPV positivity was halved, immediate colposcopy referral was reduced by two thirds, but HPV persistence at 1 year retesting was substantially similar to that observed in women at the first round. Finally detection rate was about 10 time lower than at the first round. These data have been observed in women who were rescreened 3 to 4 years after negative HPV. Data for women rescreened after 5 years, i.e. the recommended interval since 2013, are not yet available.

References

In conclusion, data from real World practice confirmed those observed in trials and gave even better performance indicators. Intervals shorter than 5 years after a negative test lead to screen a population with incredibly low prevalence of CIN2+.

References

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00512

GRADUAL IMPLEMENTATION OF HPV-SCREENING IN NORWAY: RANDOMISATION AND REAL-WORLD EVIDENCE

09. HPV screening

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Background / Objectives

A shift of primary cervical screening from cytology to hrHPV detection introduce a major change in the technical and logistical infrastructure for screening. To develop realworld evidence for preferred cervical cancer screening strategies, we compared liquid based cytology (LBC) screening every 3 year (current screening modality) with highrisk human papilloma virus (hrHPV) testing every 5 year in Norway (health service study trial number 006_2014_10_RHS).

Results

Between February 2015 and December 2017, 185,114 women, aged 34 to 69 years, who returned for their routine, triennial cervical cancer screening were assigned hrHPVtesting (cobas® HPV Test (Roche Diagnostics)) or LBC, based on even/odd day of birth. Cervical intraepithelial neoplasia grade 2, 3 and cervical cancer (CIN2+) was detected among 58,971 women who completed their followup of a positive screening test by 2017.

Conclusion

Screening attendance by age was similar in HPVscreening and LBCscreening, being 53,6% vs 52,3% after 1st and 31,8% vs 32,4% after 2nd reminder, respectively. The proportion of screeningtest positives was 5.4% in LBCscreening and 6.5% in HPVscreening, and declined by increasing age. HPV16/18 were detected in 28% of hrHPVpositives. Compared to LBCscreening, we observed 40% more biopsies all over and 50% more CIN3+ in HPVscreening.

References

HPVscreening was well accepted and detected more precancers, suggesting that HPVscreening should replace LBCscreening. Randomized implementation of HPV-

screening allows to monitor the performance of novel technology in reallife, reassuring the overall high performance of the program and mitigating the transition. Based on the results from the randomized implementation, Norwegian health authorities have decided upon a randomized national implementation of primary HPV test from 2019 until 2022.

00549

Cervical Cancer Screening Program in Germany

09. HPV screening

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Background / Objectives

From cytology to HPV based screening - Part A: Europe : Operational experiences from transforming screening programs: lessons learned

Germany

Since 1971, opportunistic screening for cervical cancer has been established in Germany. Women above the age of 20 are offered annual Pap smears (no upper age limit). In 2008, the German Federal Ministry of Health and other organizations launched the “National Cancer Plan”, which is the basis for the Law on Cancer Screening and Registration (KFRG). The KFRG enacted in 2013 demanded the development of an S3 clinical guideline to collect all available evidence on cervical cancer screening in order to define new algorithms for screening and management of cervical dysplasia.

Results

In December 2017, 21 scientific societies and professional organizations finalized the German S3-guideline “Cervical Cancer Prevention” - with financial support from the German Cancer Aid and under scientific guidance of the German Guideline Program in Oncology (GGPO) and the Association of the Scientific Medical Societies in Germany (AWMF). 16 working groups have developed evidence-based statements and recommendations (GRADE approach) about screening, triage, management and therapy of cervical precancer, follow-up etc. Several systematic reviews have been conducted by two independent institutes (M. Arbyn, WIV-ISP, Belgium; J. Kleijnen, KSR, England) to inform the guideline.

Conclusion

The systematic guideline review and its included meta-analyses by KSR showed a better protection from cervical cancer and CIN 3+ with HPV screening than with cytological screening. Therefore, the guideline group preferentially recommended an organized HPV-based screening every 3 - 5 years for all women above 30 years with

validated HPV test systems in certified laboratories only. Women below 30-35 should be screened with cytology. In case of non-participation in the organized screening program, HPV self-sampling should be offered. The S3 guideline was published in December 2017 at http://awmf.org.

The Federal Joint Committee (G-BA) as the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, issues directives for the benefit catalogue of the statutory health insurance funds (GKV) for more than 70 million insured persons and thus specifies which services in medical care are reimbursed by the GKV.

References

The G-BA published cornerstones for future cervical cancer screening in Germany starting from 2019 with an organized screening program and invitation for women at 35 years of age with HPV-Pap co-testing at 3 yearly intervals and yearly Pap testing between 20 – 34 years.

References

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00623

Transforming to HPV screening, experience in the Netherlands

09. HPV screening

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Background / Objectives

In 2017 the Dutch cervical cancer screening programme started the implementation of primary hrHPV screening with cytology as triage test. If abnormal cells are present in HPV-positive samples, the general practitioner (GP) refers the patient to the gynaecologist. All hrHPV-positive women with cytological abnormalities (≥ ASC-US) are referred, instead of referring only women with HSIL or worse in the previous cytology-based screening programme. If there are no abnormal cells, the woman is advised to have another cytology test in six months. This second cytology test is also part of the screening programme.

Liquid-based cervical cytology specimens are taken at the GP office. Women who do not respond to the initial invitation can order a self-sampling device. In case of a hrHPV-positive self-sample, a GP-visit is needed to collect a cervical cytology specimen, because cytology is not possible on self-samples.

Results

Invitation scheme

All women who are 30, 35, 40, 50 and 60 years old receive an invitation for the population screening. At the age of 45 and 55 year, women only receive an invitation when the hrHPV test at 40 resp. 50 years of age was hrHPV-positive or not performed. Women who had a hrHPV-positive test at the age of 60, receive a final invitation at the age of 65.

All laboratories use the cobas® 4800 HPV test supplied by Roche Diagnostics (Alameda, CA, USA) to test the clinical and self-samples. As part of the assay procedure each sample is tested for the presence of human cells by amplification of the human beta-globin gene.

The Evalyn® Brush (Rovers Medical Devices, Oss, the Netherlands) is used for self-sampling. ThinPrep® (Hologic, Bedford, MA, USA) is used as transport medium for cervical cytology specimens.

Quality control in general

Another important change was the reduction of the number of laboratories from 40 to 5. The two national reference officers (one for HPV and one for cytology), chair the national quality platform with representatives of the five laboratories.

As part of the preparations towards the renewed programme, the suppliers of the HPV test and thin-layer cytology trained the employees of the laboratories. Besides, cytologists and pathologists analysed two learning sets to get used to a higher percentage of cytological abnormalities. Furthermore, there is a quality programme on HPV and Cytology on a structural basis.

Conclusion

• The participation rate was 56.9% on 31 March 2018 and 60.6% on 30 June 2018. This is not representative for the final participation.

• In the total group of screened women, 9% had a positive test result for the high-risk human papillomavirus (hrHPV).

• 6.9% of all participating women used the self-sampling kit.

References

Implementation was succesful, optimisation is, as aspected, neccesary

References

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MSS5. Pro and Con hot topics

00309

MSS 5 Pro and Con hot topics: Causal role of cutaneous HPV in skin cancer: plausible or implausible

28. HPV and associated skin diseases

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Background / Objectives

Human papillomaviruses (HPVs) infect the cutaneous or mucosal epithelia and are classified phylogenetically as genera and species. Persistent infections by the mucosal high-risk (HR) HPV types from genus alpha are associated with cancer development of the genital and upper respiratory tracts. The products of two early genes, E6 and E7, are the major HR HPV oncoproteins, being essential in all steps of the carcinogenic process. Cutaneous beta HPV types are proposed, together with ultraviolet (UV) radiation, to promote skin squamous cell carcinoma. However, in contrast to the HR HPV types, beta HPV types appear to be required only at an early stage of carcinogenesis, facilitating the accumulation of UV-induced DNA mutations. Findings in in vitro and in vivo experimental models also suggest that beta HPV types and other carcinogens may synergize in the induction of additional malignancies. Data in supporting the association of beta HPV types with human carcinogenesis will be presented.

Results

N/A

References

N/A

MSS6. Validation of HPV assays usable in primary screening

00283

ASSAYS VALIDATED ON THINPREP MEDIA IN VALGENT-3

08. HPV testing

M. Poljak, A. Ostrbenk

Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana - Ljubljana (Slovenia)

Background / Objectives

In 2012, the VALidation of human papillomavirus (HPV) GENotyping Tests (VALGENT) framework was initiated to provide comprehensive evidence of the performance of HPV tests used in primary HPV screening setting and to assess the comparative performance of HPV tests with limited, extended or full genotyping ability.

Results

The VALGENT-3 study panel comprises of 1,300 samples that were obtained from 25-64 years old women that participated in the organized national cervical cancer screening program in Slovenia (screening population), enriched with 300 cytological abnormal samples (ASC-US, LSIL, HSIL). HPV genotyping tests that enable detection of more than 13 hrHPV types were designated as positive only if one of the 13 hrHPV types also included in the Hybrid Capture 2 (HC2) was detected (marked with *).

Conclusion

A total of 13 HPV tests were evaluated until end of July 2018, including two standard comparators - Hybrid Capture 2 (hc2; Qiagen) and GP5+/6+ PCR with EIA & LMNX. Six HPV tests demonstrated non-inferior clinical performance compared to hc2: RealTime High Risk HPV test (Abbott), Cobas 4800 HPV Test (Roche), Anyplex II HPV HR Detection (Seegene), HPV-Risk assay (Self-Screen), 14 High-risk HPV with 16/18 Genotyping Real-time PCR Kit (Hybribio), and Linear Array HPV Genotyping Test* (Roche). Although EUROArray HPV (EUROIMMUN)* and RIATOL qPCR HPV genotyping test* exhibited lower clinical sensitivity and non-inferior clinical specificity and non-inferior clinical sensitivity and lower clinical specificity compared to hc2, respectively, their clinical performance became non-inferior compared to hc2 when post-hoc optimized cut-offs were consider. As expected, all three genotyping assays: INNO-LiPA HPV Genotyping Extra II* (Fujirebio), Anyplex II HPV28 Detection* (Seegene), and 21 HPV GenoArray Diagnostic Kit* (Hybribio), demonstrated non-

inferior clinical sensitivity, but statistically significant lower clinical specificity compared to hc2.

References

To date, VALGENT-3 presents the largest international, head-to-head comparison of most important HPV tests currently available on the market and provides valuable data on their clinical accuracy on ThinPrep media. In addition, VALGENT-3 represents extremely valuable collection for genotype-specific comparison of several widely used HPV tests with extended or full genotyping ability, which will enable assessment of the agreement between these HPV genotyping tests and gave an insight for possible future recommendations for HPV genotyping in screening guidelines algorithms.

00563

HPV assays on SurePath media in VALGENT4

08. HPV testing

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Background / Objectives

The VALidation of HPV GENotyping Tests (VALGENT) is an international initiative designed to validate HPV assays with genotyping capabilities. Clinical performance of 14 HPV assays with varying degrees of genotyping capabilities are being evaluated within the fourth iteration of VALGENT (VALGENT4) for use in primary screening for cervical cancer.

Results

The VALGENT4 panel consists of 1,297 samples, 998 consecutive samples from routine screening enriched with 299 cytological abnormal samples. All samples were collected in SurePath from women aged 30-59 years who participated in the Danish cervical cancer screening program. A new level of panel sample quality assessment was introduced, to allow for a more precise performance comparison between assays evaluated, using the human beta globin (HBB) control of the BD Onclarity HPV assay (Onclarity) and overall DNA content and composition using the Exome iPLEX assay (Agena Bioscience) to quality assess the panel. The main objective was to verify non-inferior sensitivity and specificity of hrHPV testing with each assay compared to GP5+/6+ PCR LMNX (standard comparator test) to detect CIN2+.

Conclusion

The relative cellularity (mean CT value of HBB from the Onclarity) on the 1,297 SurePath samples (CT=24.8) was compared with 293 un-manipulated routine cytology screening samples (CT=23.8), and using the Exome iPLEX pro assay, which reports amplifiable copies on individual samples, we found a slightly lower number of amplifiable DNA copies in the VALGENT4 panel samples compared to routine extracted cervical DNA samples (ratio 0.7, $p<0.001$).

At present, assessment result of 8 tests are available. The sensitivity of Onclarity, Agena HPV MassArray assay (MA-HPV), Genomica CLART HPV4S assay (Clart4S),

Roche Cobas 4800 HPV test (Cobas), modified GP5+/6+-PCR-LMNX, Liferiver Harmonia HPV assay (Harmonia), Liferiver Venus HPV assay (Venus) and HPV Risk assay (HPVRisk) for the detection of CIN2+ and CIN3+ was non-inferior to the comparator test. Non-inferior specificity was demonstrated by Onclarity, Cobas, modified GP5+/6+-PCR-LMNX, HPVRisk and Harmonia (with application of a posteriori optimized cut-offs).

References

Together, these quality assessment data documents the quality of the individual samples and the panel. Onclarity, Cobas, modified GP5+/6+-PCR-LMNX, HPVRisk and Harmonia (with application of a posteriori optimized cut-offs) fulfil clinical cross-sectional accuracy criteria of HPV tests for use in primary screening for cervical cancer.

MSS7. Molecular signatures of precancerous lesions: Changing paradigm of early detection

00185

DNA METHYLATION MARKERS FOR THE DETECTION OF CIN2/3 AND CERVICAL CANCER IN SELF-SAMPLES AND URINE

12. Molecular markers

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Background / Objectives

Cervical cancer is associated with a persistent infection with high-risk HPV and develops through precancerous lesions (high-grade cervical intraepithelial neoplasia; CIN2/3). CIN2/3 is however a heterogeneous disease, with only a subset having a high cancer risk. CIN2/3 are characterized by overexpression of the viral oncogenes E6 and E7 in proliferating cells, which may lead to an accumulation of genetic and epigenetic changes in the host cell genome and drive progression to cancer. The epigenetic changes include DNA methylation of host cell tumor suppressor genes and result in gene silencing. This suggests that accumulating DNA aberrations in CIN2/3 are indicative of a high cancer progression risk [1].

Current screening and treatment strategies aim at CIN2/3, irrespective of the molecular signature, and result in overreferral and overtreatment of non-progressive lesions. Hence, particularly with the introduction of primary hrHPV testing in cervical screening, there is an urgent need for objective triage markers that identify clinically relevant CIN2/3 lesions in need of treatment. We show that host cell DNA methylation events provide such promising markers for the management of hrHPV-positive women. These methylation markers can be applied to cervical scrapes, as well as self-collected cervico-vaginal specimens (self-samples) and urine, increasing screening uptake and enabling full molecular screening.

Results

Targeted and genome wide methylation discovery screens were performed on hrHPV-transformed cell lines, cervical tissue specimens and self-samples. Candidate methylation markers were tested by quantitative methylation-specific PCR (MSP) on cervical scrapes, self-samples and urine.

Conclusion

We identified a series of candidate methylation target genes, of which the methylation levels showed a significant increase with severity of cervical disease ($p<0.005$) [2,3,4]. All cancers and a subset of CIN3 (70%) and CIN2 (50%) were characterized by a so-called methylation-high pattern, suggestive for a higher cancer risk. Clinical validation studies on HPV-positive cervical scrapes and self-samples specimens showed that specific methylation marker panels (e.g. FAM19A4/miR124-2) enable the detection of all cancers and clinically relevant CIN2/3 lesions, characterized by a persistent HPV infection with a duration of >5 years [2]. Interestingly, methylation markers also enable the detection of cervical cancer and a subset of CIN2/3 lesions using urine samples.

References

Host cell DNA methylation analysis provides an attractive triage tool for hrHPV-positive women, which is particularly useful for self-samples and urine. Triage by methylation markers specifically detects cervical lesions in need of treatment and can prevent overtreatment of non-progressive lesions.

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00579
DNA Methylation

19. New technologies

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Background / Objectives

There is a well-defined premalignant phase in HPV carcinogenesis, which makes HPV infection tractable to effective cancer prevention efforts and the study of molecular mechanisms involved in precancer progression to frank invasive cancer. When HPV infection becomes persistent there is an increased chance of high grade cervical intraepithelial neoplasia (CIN3). It can take 10 to 15 years of persistent HPV infection to develop invasive cervical cancer. A clearer understanding of the molecular changes during HPV persistence leading to CIN3 and early cancer has provided more accurate biomarkers for diagnosis and prognosis and allows better informed consideration of preferential druggable targets for effective non-surgical elimination or stalling of persistent HPV infections.

Results

Review of the literature and personal publications.

Conclusion

We have shown by means of methylation signatures that CIN1 is not a pre-cancer and that CIN3 can evolve directly from normal HPV-infected epithelium. We used epigenetic markers and HPV typing to investigate two main models of precancerous cervical disease progression in areas of cervical lesions with discrete coexisting foci of different grades. Methylation of tumor suppressor gene EPB41L3 and the viral regions of HPV16-L1/L2, HPV18-L2, HPV31-L1 and HPV33-L2 were determined by a highly accurate quantitative pyrosequencing of bisulfite converted DNA. There was a significant trend of increased methylation with disease grade comparing normal to CIN1 and CIN3 ($p<0.0001$). CIN1 adjacent to CIN3 predominantly shared the same HPV types as the CIN3, however, methylation differed substantially between adjacent-CIN1 and CIN3 ($p=0.008$). In contrast, diagnostically principal-CIN1 (no adjacent CIN3 detectable) had an indistinguishable methylation distribution compared to CIN1 that was adjacent to CIN3 ($p>0.1$). Our results suggest that progression from normal epithelium to CIN1 or CIN3 is usually promoted by the same

HPV type but occurs via distinct DNA epigenotypes. These results are consistent with the very good performance of the S5 methylation classifier as a triage for HPV+ women. S5 has: 1) high sensitivity and positive predictive value for CIN3; 2) predicts which CIN2 progress to CIN3; and 3) detects all cervical cancers years before diagnosis.

References

The implications of our results are profound and suggest that cervical cancer is predominantly or perhaps solely an epigenetic disease. The accurate S5 biomarker signature will directly impact on persistent HPV infections by allowing a more refined approach to follow-up and treatment options.

00310

ORAL GARGLE HPV 16 AND EPB41L3 METHYLATION:

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Oropharyngeal cancer (OPC) incidence is significantly increasing among men. With no proven method for early detection, OPCs are typically diagnosed late requiring intensive therapy that may cause significant morbidity and disabilities. To increase survival and reduce morbidity following diagnosis, an early detection screening test that can be implemented as part of routine care is urgently needed. HPV-related OPC is predominantly caused by HPV 16. We hypothesized that oral HPV 16 L1, L2, and E2 methylation and EPB41L3 methylation reflect tumor biomarker status and distinguishes OPC cases from controls.

Results

A case control study of 101 pre-treatment male OPC cases and 101 controls age and smoking history matched 1:1 to cases was conducted. Oral gargles were collected from cases and controls, and FFPE from cases. The HPV SP10-LiPA25 assay was utilized for HPV genotyping of all specimens. Methylation of three CpG sites (438, 427 and 425) in the EPB41L3 gene, and methylation status of the L1 (6367, 6389), L2 (4257, 4262, 4266, 4269, 4275, 4282), and E2 CpG sites of HPV 16 positive specimens was assessed by pyrosequencing. The Spearman correlation coefficient was calculated to assess EPB41L3 oral gargle, tumor correlations. Kruskal-Wallis test was used to compare the mean value of EPB41L3 methylation in oral gargles comparing stage I/II and stage III/IV cases versus controls, and post-hoc analysis

Dunn’s test was used for pair-wise comparisons. Receiver operating characteristic (ROC) curves were generated combining HPV 16 gene (L1, L2, or E2) methylation and EPB41L3 methylation levels. Youden’s J (J statistic) was calculated to identify the cut-point yielding the highest sum value for sensitivity and specificity. All analyses were performed in SAS 9.3.

Conclusion

Among cases, significant correlations were observed between tumor and oral specimens for all methylation biomarkers assessed ($p<0.01$). Oral EPB41L3 and HPV 16 L1, L2, and E2 methylation were significantly ($p<0.0001$) higher among cases than controls, regardless of tumor stage. In addition, statistically significant differences ($p<0.001$) in EPB41L3 and HPV 16 L1, L2, and E2 methylation were observed when comparing early stage cases (stages I/II) vs controls. When methylation of HPV 16 genes and EPB41L3 were combined 72% sensitivity and 89% specificity for the detection of OPC was observed.

References

With only two biomarkers tested at one time point, this oral gargle panel demonstrated robust sensitivity and specificity for early OPC detection. Future studies are needed to inform additional biomarkers that can maximize specificity and sensitivity of early OPC detection.

MSS8. Self-sampling: operational experiences under HPV self-sampling in an organized cervical cancer screening program

00232

HPV DETECTION IN SELF-SAMPLES: AN UPDATED META-ANALYSIS ON TEST ACCURACY AND POTENTIAL TO REACH UNDER-SCREENED WOMEN

09. HPV screening

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Background / Objectives

To respond to requests from different national screening programs to keep up-to-date evidence regarding performance of HPV testing on self-samples. To extend previous meta-analyses on: 1) accuracy of HPV testing on self- vs clinician-taken samples to detect CIN2+; 2) efficacy of offering self-sampling kits vs control interventions to reach under-screened women.

Results

Methods described in Arbyn, Lancet2017 and Verdoodt EJC2015 were applied to update prior published systematic reviews including new references published up to 15 April 2018.

Conclusion

56 accuracy studies and 25 randomized participation trials were included.

Signal-amplification based hrHPV tests were less accurate on self-samples (relative sensitivity and specificity for CIN2+ significantly <1). However, clinically validated PCR-based assays were as sensitive (ratio=0.99, CI 0.97-1.02) and slightly less specific (ratio=0.98, CI 0.97-0.99) on self-samples. Subgroup analyses did not reveal significant effects related to the self-sample device or storage media.

On average, 19% (range 6-34%) of under-screened women who received a self-sample kit at home returned it to the laboratory, whereas 11% (range 2-26%) of women in control arm had a specimen taken by a clinician, yielding a pooled participation ratio of 1.87 (CI 1.43-2.44). Opt-in self-sample strategies were less effective than mail-to-all strategies.

References

Under the condition of using validated PCR-based assays, hrHPV testing on self-samples is as accurate as on clinician-taken samples. Offering self-sampling kits generally is more effective in reaching under-screened women than sending invitations. However, response rates are highly variable among settings and therefore pilots should be set up before regional/national roll-out of self-sampling strategies.

References

KEYWORDS: cervical cancer; HPV; self-sampling, diagnostic test accuracy; screening coverage, randomised trials, meta-analysis

00632

Increasing cervical screening participation among long-term non-attenders: A randomized health services study in Sweden using e-Health

09. HPV screening

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Background / Objectives

Although screening coverage in Sweden is very high, a limited group of women never attend. Our primary objective was to determine an effective strategy reaching this group and increasing population participation in organized cervical screening.

Methods

We implemented a randomized health services study comparing 4 strategies. A random selection of 8000 women who had not attended organized cervical screening in 10 years were randomized to either 1) being sent a HPV self-sampling kit directly 2) an invitation to order a HPV self-sampling kit 3) an invitation to call a coordinating midwife with questions and concerns; or 4) standard annual renewed invitation letter with pre-booked appointment time (routine practice).

Results

Overall participation, by arm, was: 1) 18.7%; 2) 10.7%; 3) 1.9%; and 4) 1.7%. The relative risk of participation in arm 1 was 11.0 (95% CI 7.8-15.5), 6.3 (95% CI 4.4-8.9) in arm 2, and 1.1 (95% CI 0.7-1.7) in arm 3, compared to routine practice/arm 4.

High-risk HPV prevalence among women who returned kits in study arms 1 and 2 was 12.2% and participation in the follow-up colposcopy was 68.3% (PPV for CIN2+ in histology was 39.5%).

Conclusion

Targeting long-term non-attenders to achieve increased participation in organized screening is feasible, scalable, and straight-forward to evaluate. The methods should be applicable also in diverse resource settings.

00356

EVALUATION OF CLINICAL SENSITIVITY IN DRY AND WET VAGINAL SELF-COLLECTION COMPARED TO CONVENTIONAL SAMPLING AND MOLECULAR TRIAGE OF HPV POSITIVE WOMEN IN A SCREENING SETTING

10. Self-sampling

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Background / Objectives

The aim of this study is to evaluate whether self-sampling can increase screening attendance of women who do not attend HPV regular screening in Italy, to guarantee the same clinical sensitivity of the HPV test performed as clinician samples and to evaluate the perfomance of molecular triage in a screening setting. The study is founded by Regional Institute of Cancer (public health institution).

Results

About 8000 women aged between 36-64 years old who have not responded to HPV screening program were randomised in 3 groups to receive a self sampling device at home (wet-self sampling device or dry- self sampling device) or a new invitation for regular HPV screening (control group). In the self sampling arms, HPV positive women were sent directly to colposcopy and perfomed also molecular triage tests by HPV genotyping and methylation of CpG-islands of human CADM1, MAL,hsa-miR-124-2 and FAM19A4 genes .The analytical sensitivity and reproducibility of self collected samples compared to conventional were investigated using calibrator (5000 HPV16/ reaction) and the LOD (Detection Limit) was analyzed in 20 replicates.

Conclusion

In the control arm, 17% of women responded participating in the screening program while the compliance in the self-sampling group was 18.5%, without differences between wet or dry self sampling device. HPV positivity was 8.4% in the control arm, 10.5% in the dry-self sampling and 12% in the wet-self sampling group. In self-sampling group the compliance to colposcopy was 79% while in the control arm was 85%. CADM1 and MAL resulted positive in several CIN2+ lesions but also in CIN1 lesions and negative samples; no hypermethylation of FAM19A4 was observed in CIN2 cases. No difference resulted in HPV types distribution between CIN2+ and negative samples.

References

The participation in cervical cancer screening for women who have been offered a self-sampling test was a little higher compared to those who received the specimen collection device by a clinician. The methylation triage was very time-consuming because most of samples needs to be repeated for a low quantity of DNA after bisulfite conversion and viral methylation is not easy to apply because the samples had multiple HPV co-infections.

00592

Efficacy, effectiveness and perception of vaginal self-sampling strategies in a cervical cancer screening program in France : the APACHE studies

10. Self-sampling

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Background / Objectives

Cervical cancer screening coverage remains insufficient in most countries. Vaginal self-sampling for high-risk human papillomavirus testing is an acurate and promising alternative to reach unscreened women. After a first randomised control trial (RCT) to evaluate the accuracy of vaginal self-sampling with a dry swab conducted in 2009 (APACHE-1), we conducted 2 RCTs between 2012 and 2016 (APACHE-2 AND 3) to evaluate efficacy, cost-effectiveness and perception of two strategies offering vaginal self-sampling with a dry swab to increase participation among unscreened women in a cervical cancer screening program in France.

Results

Eligible participants were unscreened women aged 30–65 years, living in a French region covered by a screening programme, who had not responded to an initial invitation 9 months ago to have a Pap smear .

APACHE-2. In 2012, 6000 eligible women were equally randomised to three groups: ‘no intervention’; ‘recall’, women received a letter to have a Pap smear; and ‘self-sampling’, women received a free self-sampling kit to return to a centralised virology laboratory for PCR-based HPV testing. Efficacy and cost-effectiveness analysis were performed.

APACHE-3. In 2015, 3612 eligible women were equally randomised to two groups: 'GP delivery', women received a letter inviting them to consult their referring GP to collect a vaginal self-sampling kit (or have a pap smear) and 'home delivery', women received a vaginal self-sampling kit directly at home. Efficacy and cost-effectiveness

analysis were performed. A sample of 17 women were recalled to evaluate their perception.

Conclusion

APACHE-2. Participation was higher in the ‘self-sampling’ group than in the ‘no intervention’ group (22.5% vs 9.9%) and ‘recall’ group (11.7%). The ICER per extra screened woman was 77.8€ and 63.2€ for the ‘recall’ and ‘self-sampling’ groups, respectively, relative to the ‘no intervention’ group.

APACHE-3. Participation was higher in the 'home delivery' group (27.9%) than in the 'GP delivery' group (14.9%). Despite a higher overall cost, the cost-effectiveness ratio was lower in the 'home delivery' group (56€ vs 60€). Women appreciated the ease of access of home-mailed self-sampling kit and their autonomy to perform their own screening; some women doubted their own ability to correctly perform the self-sampling.

References

Offering an in-home, return-mail kit for vaginal self-sampling with a cheap dry swab is more effective and cost-effective than a 1) recall letter to have a pap smear or 2) 'GP delivery' in increasing participation in cervical cancer screening. Further work need to be conducted to optimize the efficiency of home-mailed self-sampling strategies and to reassure women on their ability to correctly perform vaginal self-sampling.

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MSS9. Screening in HPV vaccinated cohorts: do we know how?

00303

Screening in HPV Vaccinated cohorts: do we know how?
Cervical cancer screening in immunized populations

09. HPV screening

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Background / Objectives

There is large agreement in the scientific community about the need to re-think screening in vaccinated women, but most guidelines still recommend the same algorithms for vaccinated and unvaccinated women. The cohorts of women who were offered Human papillomavirus (HPV) vaccination in pre-adolescence are now reaching the age for cervical cancer (CC) screening in many countries. At the same time many screening programs are now shifting from Pap test to HPV as primary test. The simultaneous shift from cytology-based screening to HPV test-based screening gives the opportunity for unprecedented reorganisation of CC prevention.

Results

The National Screening Monitoring Centre and the Italian Group for Cervical Screening, following a commitment by Italian the Ministry of Health (MoH), identified the consensus conference as the most suitable method for addressing this topic. The objective was defining the best screening methods in girls vaccinated against HPV and the knowledge needs for defining future evidence-based screening strategies. During the consensus conference a Jury made recommendations about questions and proposals formulated by a panel of experts representative of Italian scientific societies involved in CC prevention and based on systematic reviews.

Conclusion

The Jury considered changing the screening protocols for girls vaccinated before their fourteenth year as appropriate. Tailored screening protocols based on vaccination status could be replaced by “one size fits all” protocols only when a herd immunity effect has been reached. Vaccinated women should start screening at age 30, instead of 25, with HPV test. Furthermore, there is a strong rationale for applying longer intervals for re-screening HPV negative women than the currently recommended 5 years, but research is needed to determine the optimal screening time points. For non-vaccinated women and for women vaccinated in their fifteenth year or later, the current protocol should be kept.

An updated review of the recommendations about screening in vaccinated girls by Scientific Societies and Governmental Agencies will be presented.

References

Conclusions and further actions

The MoH funded an HTA program to assess new screening protocols in the HPV vaccine era proposed during a Consensus conference in terms of budget impact, cost-effectiveness, organizational impact, social, ethical and legal issues. Furthermore, a cohort study for determining safe intervals in vaccinated women has been designed and is now being evaluated by the relevant Ethical Committees.

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SS1. Changing minds about HPV latency

00546

Epidemiologic Issues in HPV Latency

02. Epidemiology and natural history

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Background / Objectives

The majority (90%) of new HPV infections become undetectable within one to two years. However, a key area of uncertainty in HPV natural history models is whether an infection that becomes undetectable has truly cleared, or whether the virus persists below detectable levels or has entered a latent state. Data from observational studies suggests that re-detection of the same HPV type after apparent clearance occurs in 10–20% of women. These re-detections may represent new acquisition or recurrent detection of prior infection. Epidemiologic data from longitudinal studies of women transitioning in and out of HPV detectability (e.g., immunocompromised, sexually abstinent women) support the phenomenon of re-detection of prior infection. More recently, epidemiologic cohort studies of mid-adult women have helped to elucidate the relative proportion of new HPV detections that result from new acquisition from new sex partners versus re-detection of prior infection. Data from these studies indicate that while acquiring new sex partners remains a risk factor for new infection, the ratio of detectable HPV that is attributable to prior versus new infection increases with increasing age. Another unresolved issue is whether serum antibodies from natural HPV infection protect against re-infection with the same HPV type. Analyses of placebo arm data from HPV vaccine trials have been used to suggest that detection of natural antibodies provides protection against type-specific re-infection, but that protection may wane with age – an important consideration, however, is that the apparent lack of protection from natural antibodies in the older age groups in these studies may be explained by reactivation or re-detection of prior infection, rather than by re-infection from new partners. In this presentation, data from key epidemiologic studies addressing issues of HPV latency will be reviewed, highlighting study design considerations and remaining areas of uncertainty. Understanding HPV latency and the frequency and probability of transitions across HPV natural history states has important implications for prophylactic HPV vaccination recommendations in expanded age cohorts and clinical counseling for women undergoing HPV testing in routine cervical cancer screening.

00481

CERVICAL CARCINOGENESIS AND OCCULT CIN3: EVIDENCE FROM THE ARTISTIC TRIAL AND ENGLISH CERVICAL CANCER TRENDS, AND IMPLICATIONS FOR HPV SCREENING

09. HPV screening

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Background / Objectives

HPV testing is replacing cytology in primary cervical screening in several countries including the UK, but it is not clear from what age and how frequently women should be screened, or whether current HPV tests are sensitive enough to detect occult CIN3.

Results

CIN3 and cervical cancer incidence were analysed in the 15-year follow-up of 24,496 women in the ARTISTIC trial of Hybrid Capture 2 (HC2) HPV screening. Stored cervical samples from women who subsequently developed cervical cancer were also HPV tested by PCR (Roche Line Blot or Genera).

Cervical cancer incidence rates from 1973 to 2016 in English birth cohorts were modelled on the following assumptions:

1. The cervical cancer incidence rate remains constant in women with long-lasting CIN3. Transient CIN3, if it exists, causes a negligible cancer risk.

2. CIN3 usually develops soon after a new HPV infection and is often missed by cytology.

Conclusion

English cervical cancer rates since 1973 were predicted with remarkable accuracy from the age-distribution of HPV infection in ARTISTIC and the age of each birth cohort in 1988 when the NHS cervical screening programme began. Ten women with

prevalent cervical cancer diagnosed at entry to ARTISTIC were all HPV PCR positive (9 HC2+, 1 HC2-) with moderate (1) or worse (9) cytology. Twelve (92%) entry samples from 13 women with cervical cancer diagnosed 4-13 years after entry were HPV PCR positive, eight (62%) were HC2+ and only two (15%) were cytologically abnormal.

References

Our findings contradict several assumptions underpinning cervical screening policy and explain the unexpected increase in English cervical cancer incidence after the screening age was raised to 25 in 2004. The natural history of progression from new HPV infection to cervical cancer is age-independent. Cytology has low sensitivity for CIN3 (~40%) so diagnosis is incomplete and delayed. Models calibrated to observed CIN3 rates are therefore misleading. The long-term cancer risk is highest in cytologically normal women with occult CIN3 who shed little HPV DNA, and are often missed by HC2 and perhaps by other current HPV tests. The reporting threshold for HPV tests should be calibrated to long-term cancer risk instead of short-term CIN3 diagnosis. Triage of HPV+ women by cytology and colposcopically directed biopsy also has inadequate sensitivity. A sensitive PCR test in all post-menopausal women with curative treatment for positive cases could prevent most of the 80% of cervical cancer deaths in developing countries that occur after age 45.

00572
Methylation

16. Methylation

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Background / Objectives

Almost all HPV infections are measurably transient, however, when HPV becomes persistent there is an increased chance of high grade cervical intraepithelial neoplasia (CIN3), which can develop into invasive cervical cancer over a period of 10+ years. Considering: 1) the high prevalence of HPV infection in the general population; 2) the low probability of any given HPV infection becoming cancerous; and 3) the physical and emotional risks of surgical treatment, the biggest challenge today is how best to triage HPV-infected patients to colposcopy and treatment versus active surveillance or return to screening. Biomarkers have a key role in triage algorithms and make possible the most efficient combinations of resource utilization and disease prevention.

Results

Review of the methylation literature combined with careful consideration of personal experience and data generated by my molecular epidemiology team.

Conclusion

The most commonly used triage modality today is cytology. DNA methylation is a newer kind of biomarker measured by dedicated instrumentation. The key change in methylation is the addition of a methyl group to the 5-position of cytosine in a CpG motif. This change has profound consequences on the regulation and stability of DNA. When methylation is not correctly represented in the genome it can severely damage tumor suppressor genes and lead to many kinds of major chromosomal damage.

A strong and highly significant association is observed between DNA methylation patterns and CIN of various grades in both cervical scrapes and biopsies. DNA methylation in normal cervical epithelium and low-grade disease is generally absent or low. In contrast increased methylation is observed in patients with advanced CIN and very high levels are seen in carcinoma. These observations have been validated

in many large studies in different countries and led to the development of clinically relevant DNA methylation classifiers such as S5 composed of HPV and host genes, as well as various other proposed classifiers composed of only host gene targets. A growing role of DNA methylation testing is related to the definition of HPV persistence (by means of epigenetic signatures) and to the determination of treatment options.

References

DNA methylation plays a fundamental role in human health and disease and is a key process for orchestrating the development, growth and ageing of the body and mind. There is an abundance of accurate biomarkers to be discovered and many have already been formulated into signatures for diagnosis, prognosis and prediction of cancer outcomes.

SS3. Two vs one dose vaccine schedules: assessing the evidence

00565

POPULATION HEALTH AND ECONOMIC BENEFITS OF SINGLE-DOSE HPV VACCINATION IN UGANDA

05. HPV prophylactic vaccines

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Background / Objectives

The WHO recommends a 2-dose HPV vaccination schedule for girls aged 9–14 years, yet several studies have demonstrated similar protection with one dose. Our objective was to project the long-term health and economic impacts of routine one-dose HPV vaccination compared to 1) no vaccination and 2) two-dose HPV vaccination in Uganda.

Results

We used a three-tiered hybrid modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project long-term health and economic outcomes associated with routine (age 9 years) one-dose HPV vaccination (assuming 80% efficacy against HPV-16/18 infections under four waning scenarios) and two-dose HPV vaccination (assuming 100% efficacy over the lifetime) in Uganda. Costs included the vaccine program costs (dosage and delivery) and cervical cancer costs over the 30-year vaccination program period for the population of Ugandan women born before 2039. Incremental cost-effectiveness ratios (i.e., cost per disability-adjusted life years [DALY] averted) were calculated and compared against the Ugandan per-capita gross domestic product (GDP). Strategies less than 1x the Ugandan per-capita GDP were considered very cost-effective.

Conclusion

Routine one-dose HPV vaccination of 9-year-old girls (regardless of waning scenario) was considered very cost-effective compared to no vaccination when accounting for the cost-offsets from future cancers averted. Over the lifetimes of all Ugandan women born before 2038, one-dose vaccination averted ~30% fewer cases than two-dose vaccination but required only half the upfront economic investment. Compared to one-dose vaccination, vaccination with two doses had an attractive cost-effectiveness profile even if one-dose vaccination enabled higher coverage (90% vs. 70%) and did not wane.

References

One-dose HPV vaccination was considered very cost-effective compared to no vaccination, but was unlikely to be considered cost-effective compared to two-dose vaccination even under an optimistic waning scenario and higher coverage with differential outreach programs (90% vs 70%) could be achieved.

00567

EFFICACY OF SINGLE DOSE OF QUADRIVALENT HPV VACCINE IN GIRLS AGED 10 TO 18 YEARS AGAINST INCIDENT AND PERSISTENT HPV INFECTIONS

05. HPV prophylactic vaccines

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Background / Objectives

An affordable HPV vaccine will pave the way for the elimination of cervical cancer. The robust and durable antibody response against the targeted HPV types, the stronger immune response observed in adolescent girls and boys and the protective effect of a single dose observed in the subjects unable to complete three doses of the vaccine in the pivotal efficacy trials provided ample justification to evaluate single dose of the vaccine in the adolescent girls. An ongoing multi-centric study in India aims to evaluate the efficacy of single dose of quadrivalent HPV vaccine against incident persistent HPV infections and cervical neoplasias.

Results

IARC initiated a randomized trial in September 2009 to compare the efficacy of two vs. three doses of the quadrivalent HPV vaccine in unmarried 10-18 year old girls. The Government of India stopped vaccination in all HPV vaccine trials in April 2010 due to reasons unrelated to this study. The suspension resulted in 4348 girls receiving 3 doses per protocol (days 1, 60 and ≥180), 4979 receiving 2 doses per protocol (days 1 and ≥180), 3452 receiving 2 doses at days 1 and 60 by default, and 4950 receiving one dose by default. An age and site-matched cohort of 1540 unvaccinated married women was recruited in 2011 as unvaccinated controls. Plasma samples were collected for immunogenicity studies at baseline and at various timepoints post-vaccination. The first cervical sample for HPV genotyping was collected from each participant 18 months after marriage or 6 months after first childbirth (whichever earlier) and yearly thereafter. For each unvaccinated woman,

first cervical sample was collected at study entry and yearly thereafter. Married women aged 25+ years are screened with HPV test.

Conclusion

All vaccinated girls seroconverted against HPV 16/18 and all remained seropositive at 48 months regardless of number of doses. The frequency of cumulative incident HPV 16/18 infections over eight years from vaccination was much lower in single dose recipients (1.7%) compared to unvaccinated women (7.0%). The rates of incident persistent infection (defined as detection of same HPV type in two consecutive samples collected at least at 10 months interval) in 4,000 vaccinated and 1,219 unvaccinated women providing at least two samples suggest high efficacy against persistent HPV 16/18 infections, regardless of number of doses. There was a total of five (0.1%) persistent HPV 18 infections and no persistent HPV 16 infection among the vaccine recipients compared to 21 (1.7%) persistent infections with HPV 16/18 among unvaccinated women. No persistent HPV 16/18 infection was detected in 1288 single dose recipients. No cervical neoplasias detected in the vaccinated participants till date.

References

The early efficacy results of single dose are encouraging.

SS4. HPV 6-11: low risk HPV infection and disease - Anogenital versus Oral

00606

Impact of HPV vaccine on HPV 6/11 at a population level

05. HPV prophylactic vaccines

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Background / Objectives

To review data regarding the impact of HPV vaccines on HPV 6/11 inefctions at a population level

Results

Literature review

Conclusion

There is now a wealth of evidence showing that the introduction of the quadrivalent HPV vaccine has led to a reduction in anogenital warts in many countries [1]. Very recent data also shows reductions in cases of laryngeal papillomatosis in Australia and Canada. Modelling data from Australia predicts that in 40 years time there will be an ~98% reduction of in anogenital warts cases in Australian residents, whereas ~50% of total cases will be in international travellers from countries with lower vaccination coverage.

References

Population based HPV 6/11 vaccination leads to profound decreases in cases of anogenital warts and laryngeal papillomatosis.

References

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00581
CHILD ABUSE AND HPV

09. HPV screening

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Background / Objectives

The WHO estimates that 223 million girls and boys are abused each year worldwide. Although girls predominate, it is likely that boys are vastly underreported. Perpetrators are usually those with easy access to the child- family and close friends and teachers/religious leaders. The majority of children abused do not disclose immediately rather after months of repeated abuse. One of the certain signs of abuse is the presence of an STI such as chlamydia or gonorrhea. The presence of anogenital warts (AW) is more uncertain since perinatal transmission has been reported. AW in children < 18 months is more often associated with perinatal transmission, however, sexual abuse (SA) in non-verbal children is difficult to establish. Most SA cases do not result in obvious physical signs since abuse often takes place in fondling or rubbing of genitals. In children >3 years, the risk of SA increases with each year of age. Detection of HPV DNA from urine from children has also been associated with increased risk of sexual abuse. Detection of HPV from the cervix of abused prepubertal girls is difficult because invasive pelvic exams are not routine in evaluations. There is data to suggest that women SA as children are at increased risk of cervical cancer (CC) suggesting cervical HPV infections occur even if no penetration is reported. With the onset of puberty, there are changes of the cervix with epithelial differentiation and cell replication which may establish these infections in vulnerable stem cell populations which are at risk for transformation into CC. It is also plausible that the younger the child, the longer exposure to HPV persistence—a strong risk for CC. Persons with history of childhood SA often display high risk behaviors placing them at risk for new infections including unprotected sex, sexualized behaviors, and substance abuse. Evaluation of children with AW should include genital examination for signs of trauma/infection as well as eliciting history of behavior change (e.g. poor school performance, clingy behavior, sleep disturbances, fecal soiling). STI testing should be considered. In those with confirmed sexual abuse, administration of the HPV vaccine before the likelihood of engaging in high risk behaviors is recommended with some suggesting it be offered even before the age of 9 years since follow-up years later is difficult. Some suggest that this population should be screened for CC earlier than 21 years of age. However, if the patient is not yet voluntarily sexually active, the psychological harm may outweigh deferring screening until later.

SS5. Cervical cancer in central Central and Eastern Europe and Central Asia

00542

CERVICAL CANCER SCREENING PRACTICES AND CURRENT STATUS OF VACCINATION IMPLEMENTATION IN CENTRAL AND EASTERN EUROPE

36. Public health

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Background / Objectives

To review current cervical cancer screening practices and the implementation status of vaccination against HPV in Central and Eastern Europe where the burden of cervical cancer is generally higher compared to Western or Northern Europe.

Results

In 16 Central and Eastern European countries: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia and the Former Yugoslav Republic of Macedonia data were collected by surveys conducted during August–October 2011 and in January 2013. A follow-up survey is in progress to update data and provide an overview of the current situation.

Conclusion

In 2013, opportunistic and organized cervical screening, mainly based on conventional cytology was performed in nine and seven countries in the region, respectively, with the proposed age of the start of screening ranging from 20 to 30 years and the estimated coverage ranging from a few percent to over 70%. At least one current HPV prophylactic vaccine was registered in all central and eastern European countries except one. Until the end of 2013, six countries have and ten countries have not integrated the HPV vaccination into their national immunization program and provided routine vaccination free of charge to the primary target population. Vaccination of males was not recommended in any country in the region. According to the results of a survey performed by WHO Europe in 2016, in five countries from the region HPV vaccination was still not available through national vaccination programmes free of charge. An update on the current situation of cervical cancer screening practices and the implementation status of vaccination against HPV

in the region will be provided until the end of October 2018 and presented at the congress.

References

In the majority of countries where only opportunistic screening was performed, well-prepared activities have been ongoing for switching to organized screening. Despite an obvious progress in implementing HPV vaccination in the region, the success of HPV immunization programmes has varied in regard of coverage rates.

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00545

CERVICAL CANCER SCREENING PRACTICE AND CURRENT STATUS OF VACCINATION IMPLEMENTATION IN THE RUSSIAN FEDERATION Rogovskaya S, Bebneva T., Podzolkova N (Russia)

36. Public health

S. Rogovskaya [1], T. Bebneva [2], N. Podzolkova [1]

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Background / Objectives

The burden of human papillomavirus (HPV) and its associated diseases in Russia is high. Both the incidence and mortality rate of cervical cancer are getting higher last years. The incidence rate is 15.6 per 100,000. Cervical cancer is an important public health care problem.

Results

The high-risk HPV (hrHPV) prevalence among women with normal cytology ranged from 12.0% to 58.4% according to last publications. The anogenital warts (AGW) prevalence rates is not well defined and varies in regions of Russia.

Conclusion

Opportunistic screening programs, the lack of efficient call-recall systems, low coverage, and the absence of quality assured cytology with centralized screening registry are major reasons for low success rates of cervical cancer programs in Russia.

New National screening program is approved by MOH in 2017 starting in 30 years-aged women for free of charge within the national program of screening (dispanserization) of population and is being implemented actively.

HPV vaccination is currently not approved on the state level and still not included into National Calendar of immunization. The reasons are mainly due to pricing, availability, and limited awareness among public and health care providers. There are several regional vaccination programs are being organized successfully. The most comprehensive programs are in Moscow region. S-Petersburg, Khanty-Mansy region, etc.

Based on the analysis of statistical reports of the Moscow region as a result of vaccination of girls observed a reduction in the incidence of AGW in 2016 compared to 2009, from 14.2 to 5.9 (per 100 000 for girls). Based on date of the state statistics there has been a reduction in the incidence of anogenital warts in the population in the Moscow region with up 56.7 to 20.2 (per 100000 population). Nevertheless, the most important effect of vaccination in 2015 was the lack of a rise in the incidence of cervical cancer in women in the region, as well as the reduction in the incidence in young women aged 15-24 years. More than 9 000 doses of vaccine have been inserted in S-Petersburg, more than 2500 girls and boys have been vaccinated in Khanty-Mansy region.

References

Held in Russian regions the programs of HPV vaccination and cervical cancer after 10 years resulted in a reduction of HPV-associated pathology. There were no serious side-effects. It determines the need to continue vaccination programs. Country-specific research, the analysis of pilot regional programs, organized nationwide screening programs, registries and well-defined vaccination policies are needed.

SS6. Uses of new technologies in HPV vaccine behavioral science research

00285

(SS 07-03): Using mobile application strategies and social media to increase HPV vaccination rates among young men who have sex with men

19. New technologies

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Background / Objectives

The purpose of this presentation, which is a part of approved Session SS07 “Uses of New Technologies in HPV Vaccine Behavioral Science Research,” is to describe a research project that involves the innovative use of a social/sexual networking application (app) to reach yount men who have sex with men (YMSM) and encourage them to get vaccinated against HPV.

Results

Our research project developed a HPV vaccination app to guide the young men to a health center where HPV vaccine is administered. First, we trialed a social networking app based recruitment campaign to recruit YMSM for online focus groups. YMSM were recruited across 3 states [in the United States (U.S.)] in 6 days for 6 focus groups. The focus groups elicited YMSM perspectives for development of a web-enabled mobile application (app) which would enable a transfer of health information as well as provide a connection between a mobile MSM focused social network community and a local health center. Then, using these results, we collaborated with a design firm to build our study web-enabled app. This app seeks to bridge the intention-behavior gap in a youthful and culturally appropriate format that provides all of the education and resources needed for YMSM to obtain HPV vaccination. The apps components and capabilities include educational videos and text, geolocation for partnered health center, and appointment/ appointment reminders capabilities. The study app will be piloted in 1 metropolitan U.S. city, recruitment will occur on a MSM focused social networking app.

Conclusion

Topics to be covered in this presentation include: approaches to recruitment through the social/sexual networking app, the use of online focus groups to elicit preferences

for HPV vaccine app development, and how we used these preferences in collaboration with a technology design firm to build a web-enabled app that addresses HPV vaccination and other sexual health issues.

References

Today’s adolescents are redefining ways of communication and engagement. Online portals/ websites, mobile applications, and social media have become a daily part of adolescent’s lives. Recent research has documented that youth would like to rely on technology to seek out health information and engage with health providers. Participants for this session will understand effectiveness of recruitment campaigns on social media for HPV vaccine research, use of online focus groups to elicit preferences for HPV vaccine app development, and how we used these preferences in collaboration with a design firm to build a web-enabled app that addresses HPV vaccination and other sexual health issues

00421

Using electronic approaches for providing targeted and tailored health messages to young men who have sex with men through the Outsmart web-based HPV intervention

34. Health education

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Background / Objectives

Web-based approaches are a promising strategy for promoting the health of adolescents and young adults. We developed and pilot-tested a web-based HPV vaccination intervention for young gay and bisexual men (YGBM), a population at increased risk of HPV-related disease.

Results

We conducted a pilot trial of *Outsmart HPV*, a population-targeted, individually-tailored intervention to promote HPV vaccination among young gay and bisexual men (YGBM). During fall 2016, we used Facebook advertisements ("ads") to recruit 150 unvaccinated YGBM aged 18-25 years from the United States. A 4x2x2 factorial experiment varied aspects of ads (e.g., image, content focus, disease framing). Poisson regression determined whether these experimental factors affected ad performance. Once determined to be eligible, consenting participants were randomized to receive either *Outsmart HPV* (intervention group) or standard HPV information (control group). We assessed intervention effects on vaccination outcomes using linear and logistic regression.

Conclusion

Recruitment ads that featured the image of a couple or a group of young men reached the greatest number of potential participants. Ads with text framed around preventing a sexually transmitted disease had greater engagement compared to ads framed around cancer prevention. Overall, intervention participants reported high levels of acceptability and satisfaction with the Outsmart HPV intervention (all > 4.4 on a 5-point scale). At 7-month follow-up, HPV vaccine initiation was higher among men in the intervention group than in the control group (45% vs. 26%; OR = 2.34, 95% CI: 1.18–4.67).

References

Findings from this study suggest approaches for optimizing recruitment and demonstrate the potential of *Outsmart HPV* as a technology-based strategy for increasing HPV vaccination among this population. This presentation will share lessons learned from our social media recruitment process and discuss results of the intervention’s effects on YGMS's attitudes, beliefs, and vaccination uptake.

00299

Digital Interventions to Improve HPV Vaccine Uptake: Results and Issues

36. Public health

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Background / Objectives

The uptake of the HPV vaccine among U.S. male and female adolescents in the recommended ages for vaccination remain far below the Healthy People 2020 vaccination goal of 80%. A variety of factors can account for lack of progress in U.S. HPV vaccination rates, but lack of accurate and accessible information about the HPV vaccine among parents of adolescents are likely to play a particularly important role.

Results

Digital interventions that are tailored and responsive to parental concerns and informed decision making about HPV vaccination may play a role in improving early adolescent HPV vaccination rates.

Conclusion

The development, testing and early trial data of a smartphone web app (Vacteens.org) for parents and male and female adolescents will be presented.

References

Issues of web app implementation and diffusion will be discussed.

SS7. Microbiome analysis: are we ready for clinical use?

00580

HPV PERSISTENCE AND CLEARANCE RELATED TO MICROBIOTA

17. Microbiome

A.B. Moscicki

University of California-Los Angeles - Los Angeles (United States of America)

Background / Objectives

As studies expand our knowledge of the vaginal microbiome (VM) and immune function, it appears that the VM influences the natural history of HPV from clearance to the development of cervical cancer. The loss of Lactobacillus in patients with HSIL and CC has been demonstrated in several studies. However, its role in the early natural history remains less clear. The objective of this talk is to examine the role of the vaginal microbiome and its associated cytokine and metabolomic profiles in a prospective study of HPV 16 acquisition, persistence and clearance.

Results

From a prospective study in healthy adolescent and young women, cervical samples collected from 14 women were selected at the time of HPV16 preacquisition, acquisition and persistence and clearance. Approximately 5 to 8 visits were selected for each women to reflect those 3 states. In addition, 4 visits from 8 women with no history of any HPV during the study were selected. All samples were assayed for cytokine , microbiome, and metabolomic profiling.

Conclusion

Using Markov chain modelling, we showed that women with no history of HPV were likely to remain in the same microbiome community states (CST) over time whereas women with HPV16 were more likely to transit between CSTs. No immediate VM pattern appeared to differentiate the 3 HPV 16 states. For cytokine profiles, post-clearance visits had significantly higher levels of nine inflammatory cytokines compared to samples from pre-acquisition/persistent. Samples from women with no history of HPV infection had similar cytokine profiles as clearance. In post-clearance, higher levels of IFNγ, TNF, MIP1, IL-1β were associated with Megashaera and IFNα2 was associated with Rothia. Higher levels of ILs 4, 12 and 13 were associated Streptococcus spp. Leptotrichia was also associated with several elevated cytokines. Several metabolites associated with inflammation and tumor growth had increased expression during persistence vs pre-acquisition.

References

The elevation of cytokines at clearance likely represents a successful anti-viral immune response. The similar higher levels of cytokines seen in women with no history of HPV may suggest that a certain level of inflammatory surveillance is required to maintain an HPV negative state. Therapeutics targeting certain bacterial species may be advantageous for HPV clearance in women with persistence.

00223

EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN A HIGH-RISK HPV INFECTED PATIENTS. RESULTS OF DIFFERENT STUDIES.

22. Cervical neoplasia

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Background / Objectives

A new multi-ingredient non-hormonal Coriolus versicolor-based vaginal gel has been recently commercialized in Spain to prevent and treat the HPV-dependent low grade cervical lesions. Evaluate the consistency of the effect of this gel in patients infected with high-risk HPV.

Results

Results from 3 independent observational non-comparative studies carried out in 3 different centers of Spain and preliminary results of 1 clinical trial were evaluated. One of the them was prospective (Vigo study)[1] and the other two were retrospective (Coruña and Hospitalet studies)[2,3].

Vigo study: HPV clearance at 6 months of 25 16 and/or 18 HPV infected patients older than 24 years was evaluated as a secondary endpoint.

Coruña study: A total of 57 medical records of patients with high risk HPV (mean age 38.4 years) were analyzed. HPV clearance at 6 months was evaluated as primary endpoint.

Hospitalet study: Data of 91 high risk HPV patients between 20 and 65 years. Primary endpoint: composite efficacy variable consists of percentage of patients with normal cytology and/or HPV clearance at 6 months

Patients were treated at recommended dose of vaginal gel: 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months (except menstrual days).

Conclusion

After 6 months of treatment, 48% of patients cleared HPV 16-18 (Vigo study), reduction of 58% were observed in number of high risk positive HPV patients (Coruña study) and 72.5% of patients negativized cytology and/or cleared HPV (Hospitalet study) vs baseline ($p \leq 0.0001$ for all results, Chi-square).

These results are consistent among them and with 3 months preliminary results of a phase II, randomized, open, parallel comparing the Coriolus-based vaginal gel vs wait and see approach[4]. (Figure 1)

References

Use of Coriolus-versicolor vaginal gel in clinical practice shows a significant and consistent benefit in high risk HPV clearance. Data of further observational studies and clinical trials should confirm these exciting results.

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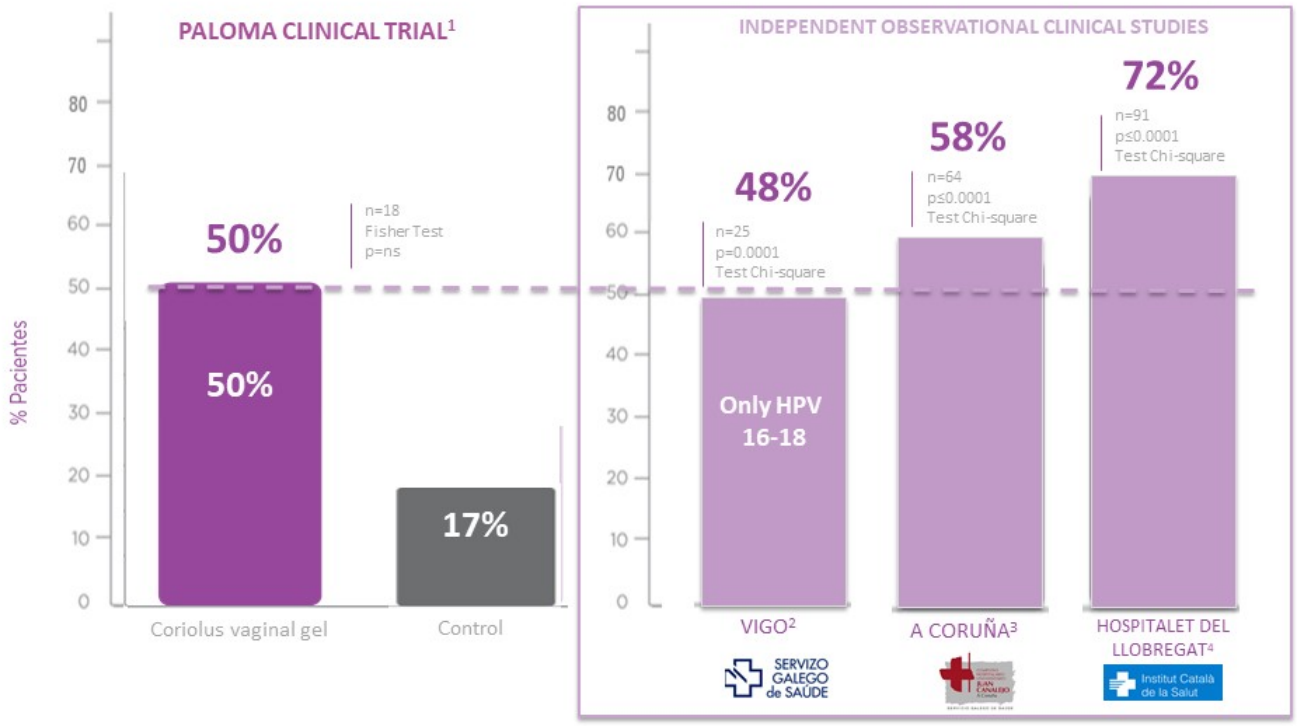
HIGH-RISK VPH CLEARANCE AT 6 MONTHS
(Paloma clinical trial vs Independent clinical studies)



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SS8. CoheaHr: Comparing Health Services interventions for the prevention of HPV-related cancer in European countries

00633

HPV testing on self-collected versus clinician-collected samples: the IMPROVE randomized diagnostic study

10. Self-sampling

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Background / Objectives

Human papillomavirus (HPV) testing on self-collected samples (HPV self-sampling) is a potential primary screening instrument, but non-inferiority as compared to HPV testing on clinician-collected samples

in the regular screening population remains to be assessed. The IMPROVE-study is a large randomised non-inferiority trial within the setting of the Dutch organized screening programme,

that aims to assess the accuracy of HPV self-sampling among screening responders.

Methods

16,410 women were randomised (1:1) to self-collection or clinician-collection. HPV-positive women were retested with the other collection method and were triaged by

two times cytology in accordance with the Dutch screening guidelines. Women were enrolled in 2015 and 2016 and histological follow-up was collected until March 2018.

The clinical end-points are CIN2+ and CIN3+

00537

Population-based effectiveness on high-grade cervical lesions of HPV vaccination

13. Screening methods

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Background / Objectives

Prevalence of high-grade cytology (HSIL) and the positive predictive value (PPV) of HSIL for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) are expected to decrease in vaccinated populations, potentially requiring changes in screening policies. In Sweden, the first partly HPV-vaccinated birth cohorts have entered the screening program, and more birth cohorts with higher vaccine coverage will enter the screening program in subsequent years.

Results

We included all women born during 1985-1993, who were resident in Sweden and alive from the introduction of HPV vaccination (1st October, 2016) to age 24 years and 6 months, in order to assess their first cytology during age 23 and the following histological diagnosis within 6-months after the index cytology. We determined the detection rate and risk ratios (RRs) with 95% confidence intervals (CIs) of HSIL that was histologically confirmed as CIN2+ among their first cytology during age 23 by registry linkage between the National Swedish Cervical Screening Registry and the HPV vaccination registers. We also calculated the PPV of HSIL for histologically confirmed CIN2+ with 95% CIs by age 24 years and 6 months, in relation to HPV vaccination in the birth cohort.

Conclusion

There was a lower detection rate of HSIL which histologically confirmed as CIN2+ for vaccinated women compared to unvaccinated women (birth cohort 1989-1992: 1.4% vs 0.6%, RR 0.60, 95% CI (0.54 - 0.66); birth cohort 1993: 1.5% vs 0.8%, RR 0.70, 95% CI (0.59 - 0.82)). PPV of HSIL for CIN2+ was decreased for vaccinated women compared to unvaccinated women (birth cohort 1989-1992: 71.0%, 95% CI (68.8%-

73.1%) vs 63.1%, 95% CI (57.6% - 68.3%); birth cohort 1993: 73.4%, 95% CI (67.6%- 78.7%) vs 65.9%, 95% CI (59.3%- 72.1%)).

References

HPV vaccinated women had lower detection rate of HSIL that was histologically confirmed as CIN2+ compared to unvaccinated women and a corresponding decrease in PPV. The decrease was rather modest, suggesting that changes to the screening program are not yet warranted and continued surveillance of the PPV for cytology (compared with the PPV of HPV screening) among HPV-vaccinated cohorts is needed.

00614

How to screen women beyond age 50: a model-based analysis

36. Public health

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Background / Objectives

The risk of CIN2/3 and invasive cervical cancer (ICC) after a negative HPV test is known to be lower than after negative cytology. However, the effect of age is not well studied

Results

We used data of 4 RCTs (NTCC, POBASCAM, ARTISTIC and Swedscreen) to compute the incidence of CIN2/3 and of ICC after a negative entry cytology in the control arm and after a negative entry HPV test in the experimental arm in women aged <50 and ≥50 years (overall 161220 women with normal baseline testing, including 736 CIN2/3 and 54 ICC).

We used a mathematical model to evaluate if low cytology sensitivity for a subset of precancerous lesions could explain the observed results. We predicted, by the model, the risk of CIN2/3 and of ICC 3 years after normal cytology in women aged 50-64 and 25-49 years, under different scenarios including or not the presence of precancerous lesions poorly detectable (i.e. sensitivity 5%) by cytology.

Conclusion

The age-adjusted relative incidence in the HPV vs. cytology arm was 0.63 (95% CI 0.54-0.73) for CIN2/3 and 0.36 (0.20-0.66) for ICC. The arm-adjusted relative incidence in women aged ≥50 vs. <50 years was 0.22 (0.16-0.30) for CIN2/3 and 1.93 (1.09-3.43) for ICC. The 3.5-year risk of CIN2/3 per 10,000 women aged < and ≥50 years was 18.7 and 5.5 respectively after a negative entry cytology and 14.5 and 3.0 respectively after a negative HPV test. The corresponding ICC risks were 1.2 and 2.5 after a negative cytology and 0.3 and 1.0 after a negative HPV test.

In model simulations, CIN2/3 risk decreased at age ≥50 under all scenarios.Likewise, assuming low sensitivity of cytology for some lesions, the predicted 3-year ICC risk increased above age 50. The older-minus-younger ICC risk difference increased from +0.8 to +2.5 and +7.4 per 100,000 if poorly detectable lesions represented 8%, 14% and 33% of precancerous lesions, respectively. In scenarios without cytologically poorly detectable lesions the predicted risk difference was -1.4. Under the scenarios that predicted ICC risk to increase at age >=50 an increased prevalence of lesions undetected from long time (>20 years) at age ≥50 was also predicted

References

The effect of HPV was similar in both age groups. However, at variance with CIN2/3, the risk of ICC increased at age ≥50. Model predictions were consistent with observations only when assuming a subgoup of CIN2/3 difficult to detect by cytology. Of note, women in the HPV arm were at their first HPV screen and had plausibly already accumulated lesions undetected by cytology. Given increased HPV sensitivity, the observed effect is expected to disappear at subsequent HPV screens.

SS9. Screening strategies for developing countries: what works and what doesn’t work

00227

SELF-SAMPLING ACCEPTABILITY IN A COMMUNITY-BASED CERVICAL CANCER SCREENING INITIATIVE: A MIXED METHODS ANALYSIS

35. Low resource settings

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Background / Objectives

To assess self-sampling acceptability and experiences among ACCESSING* participants, a feasibility study for Community Health Nurses (CHNs)-directed self-sampling and HPV testing in rural communities of the North Tongu district in Ghana.

*Adequate Cervical cancer Capacity building, Education and Screening by new Scientific Instruments in Ghana

Results

A mixed methods approach was used to evaluate self-sampling acceptability and experiences among screening participants in a rural district in Ghana. In 2015, 2000 women self-collected a sample (Evalyn brush, Rovers, Oss, The Netherlands) and filled in exit surveys. Additionally, Focus Group Discussions (FGDs) in five purposively sampled (representing urban-rural) communities were held. FGDs were held in Ewe, translated and transcribed verbatim. The interviews were analyzed according to qualitative content analysis guidelines. Ethical clearance and written informed consent were obtained for sampling and assessment of the experience.

Conclusion

1985 of 2000 women provided complete questionnaires (median age 30 years, range 18 to 65). 97.7% (1939/1985) took the sample themselves; of those, 53.7% unsupervised and 46.3% supervised by a health worker. 2.2% had the sample taken by a health worker. Of the ones that took the sample themselves, 98.2% found it “easy”

or “very easy”. 97.3% felt “very comfortable” or “somewhat comfortable”, 2.4% experienced the sample-taking as “somewhat uncomfortable” or “very uncomfortable”, six gave no answer. Of the ones that had the sample taken by a health worker, all felt “very comfortable” or “somewhat comfortable”. There was no difference between the groups in regard to comfort of sample-taking (p=0.37).

Only 3.6% indicated that they had previously been screened. 90.7% marked that they would get checked more often if the self-sampling brush works as well as going to see a doctor at a clinic to get sampled. 99.7% indicated they would prefer self-sampling if their risk is as reliably determined as by physician-directed cytobrush sampling.

In the FGDs (n=29) two mediators of acceptability emerged: respect towards health care providers that performed the study recruitment and gave the sampling instructions, and trust of well-known community health nurses.

References

Our results indicate very high acceptability of self-sampling among screening participants in the North Tongu district, Ghana, majority of whom have not been screened before. Working with CHNs may contribute to high acceptability but the social dynamics have to be taken into account to ensure informed and voluntary participation.

SS10. HPV FASTER projects worldwide

00587

THE COHEAHR-WP4 FEASIBILITY STUDY: WOULD EUROPEAN ADULT WOMEN GET HPV VACCINATED?

05. HPV prophylactic vaccines

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Background / Objectives

The success of an HPV-FASTER campaign (screen and vaccination of adult women) depends among other factors of the acceptability and vaccine uptake by the targeted population. Compliance with an invitation to receive HPV vaccination was esplored within the COHEAHR-WP4 study.

Results

The study invited women aged 25-45 from 16 recruiting sites in 9 European countries; 14 sites used opportunistic recruitment at heath care centers (Spain, France, Slovenia, France, Finland, United Kingdom and Germany) and 2 used invitation-to-participate letters to women scheduled to be visited from their screening registries (Denmark and Sweden). Participating women completed a questionnaire on demographics, clinical and screening history as well as knowledge, attitudes and reasons for acceptance/refusal of HPV vaccine. To those who accepted vaccination, HPV vaccine was offered free of charge so that uptake and compliance with three doses could be assessed.

Conclusion

Overall, 3502 women completed the questionnaire and 2602 (74.3%) accepted vaccination. By country, acceptance ranged from 97% in one site in Spain to 25% in one site in Slovenia. In countries where the study has been completed, compliance with a 3-dose schedule was over 80%. Factors influencing vaccine uptake differed by country.

References

Preliminary results suggest that HPV vaccination by adult women in screening programs is accepted. Preventive strategies including HPV screening and vaccination are worth further exploration.

References

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00571

HPV-FASTER: Modelling population-level effectiveness and cost-effectiveness in low and high-resource settings

36. Public health

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Background / Objectives

HPV-FASTER strategies, which involve extended HPV vaccine catch-up for women aged up to 45 years, could accelerate the timeline to elimination in low-middle income countries (LMIC); however, the effectiveness of such strategies compared to screening has not been determined. HPV-FASTER in high-income countries (HIC) could be integrated with existing screening programs, and vaccination could be offered to women who test HPV negative, thereby improving cost-effectiveness. I will present the predicted impact of HPV-FASTER for LMIC, and the cost-effectiveness of HPV-FASTER combined with an existing HPV-screening program for HIC, using Australia as an example HIC.

Results

We used an extensively validated platform ('Policy1-Cervix') to evaluate the impact of the quadrivalent, bivalent or nonavalent vaccine in women aged 25-45.

Conclusion

For LMIC, HPV vaccination at age 25, 35 or 45 years reduced the lifetime risk of cervical cancer mortality by 29-42%, 17-26% and 11-16%, respectively (range depends on vaccine used), and the number-needed-to-vaccinate to avert a death was 210-308, 340-510 and 540-780. Conversely, once-lifetime HPV-testing between ages 30-45 reduced cervical cancer mortality by 42-52%, and the number-needed-to-screen to avert a death was less than 300.

For HIC, compared to 5-yearly primary HPV screening in unvaccinated females, vaccination at age 25, 35 or 45 years could reduce the lifetime risk of cervical cancer mortality by 29-46%, 22-30% and 18-24%, respectively, if screening rates are unchanged in vaccinated females. Compared to 5-yearly primary HPV screening in unvaccinated females, discharging females vaccinated at ages 25, 35 or 45 years was less effective. However, referring vaccinated females to extended 10-yearly

screening has similar effectiveness, and was cost-effective provided the cost per-vaccinated-female was <40% the cost per-vaccinated-girl under the adolescent program.

References

HPV vaccination of adult women is not as effective as once lifetime HPV testing for women aged 30 and older for LMIC. In HIC, vaccinating HPV-negative women, followed by extended interval screening, could be considered provided the vaccine is supplied at less than half the price for 12-year-olds.

00613

Falsifiable modelling for cervical cancer control: an open-source option

36. Public health

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Background / Objectives

In May 2018, the Director-General of the World Health Organisation announced a call-to-action for the elimination of cervical cancer as a public health problem. National and local planning and evaluation will be essential to meet this target. Worldwide, mathematical modelling has become a standard tool in the design and assesment of public health interventions. To be reliable, model based-projections must use valid data and realistic assumptions. From that perspective, most modelling teams in high-income countries have access to the high quality sets of data and validated models essential to draw their projections. However, in most low and middle-income countries (LMIC) access to high quality sets of data modelling tools is not to be taken for granted.

Results

We have used the R, a free software environment for statistical computing (https://www.r-project.org/), to develop an open-source model of HPV transmission sufficiently flexible to be adaptable to virtually any context. We used EpiModel and Statnet suite packages (https://github.com/statnet) to model sexual behavior and HPV infection natural history and control, respectively. Using Rwanda as a study case and publically available sources of data we have developed reproducible procedures to characterize the population. HPV prevalence data, essential to calibrate model's outputs, were obtained from a recent IARC's prevalence survey.

Conclusion

We have developed an open-source agent-based model of HPV transmission accounting for demographic dynamics and sexual behavior of the population, for the natural history of HPV infection, and for the effect of HPV vaccination. We have identified a minimum set of information essential to inform model-based predictions. The model can also incorporate more complex information whenever available. We have defined transparent procedures to use data publically available source of data

such as the UN World Population Prospect and from the Demographic Health Surveys. The proposed model is capable of reproducing local demography, sexual activity patterns, and HPV epidemiology and to provide projections of the impact of vaccination in the Rwandese population.

References

The use of an open source approach and of a programming language widely diffused in the epidemiological and bio-statistical community makes all steps of the modeling process falsifiable and transparent. This is a crucial step to generate transferable scientific knowledge. We consider that access (and guidance) to open-source, validated and well-documented models to quantify the long-term medical, societal and economic benefits of vaccination and screening in LMIC is essential.

CS1. Challenging clinical topics

00231

INVOLVED MARGINS AT EXCISION: AN ACCURATE PREDICTOR OF TREATMENT OUTCOME

09. HPV screening

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Background / Objectives

Incomplete excision of cervical pre-cancer is associated with therapeutic failure and is therefore considered as a quality indicator of clinical practice. Conversely, the risk of pre-term birth is reported to correlate with size of cervical excision and therefore balancing the risk of adequate treatment with iatrogenic harm is challenging.

Results

We extended previous systematic reviews that assessed separately the risk of treatment failure associated with the margin status of the cervical excisions and the accuracy of post-treatment high-risk (hr) HPV testing to predict residual/recurrent cervical pre-cancer. Information on positive resection margins and subsequent treatment failure was pooled using procedures for meta-analysis of binomial data. The meta-analysis comparing the accuracy of the margin status with post-treatment hrHPV testing was restricted to studies with i) an average follow-up of at least 18 months post-treatment and ii) treated disease and treatment outcome were histologically confirmed cervical intra-epithelial neoplasia of grade two or worse (CIN2+).

Conclusion

The average rate of positive margins was 23% (95% confidence interval [CI] 20-26%) and varied by treatment procedure (ranging from 18% for laser conisation to 26% for large loop excision) and increased by the severity of the treated lesion. The overall risk of residual/recurrent CIN2+ was 7% (CI=5-8%). Treatment failure was 5 (CI=3.2-7.2) times greater with positive compared to negative resection margins. The risk of treatment failure was highest when the endo-cervical margin was positive.

The pooled sensitivity and specificity to predict residual/recurrent CIN2+ was 56% (CI=46-66%) and 84% (CI=79–88%), respectively, for the margin status, and 91% (CI

82-96%) and 84% (CI=77-89%), respectively, for hrHPV testing. The margin status was 41% less sensitive but not more specific than hrHPV. A negative hrHPV test post-treatment was associated with a risk of CIN2+ of 0.8%, whereas this risk was 3.7% when margins were free.

References

The risk of residual/recurrent CIN2+ is significantly greater with involved margins on excisional treatment. However, hrHPV post-treatment predicts treatment failure more accurately.

References

KEYWORDS: cervical cancer, treatment of cervical pre-cancer, outcome prediction, resection margins, human papillomavirus, diagnostic test accuracy, meta-analysis

00181

Colposcopic Terminologies, Why are they Different in Europe and North-America?

21. Colposcopy

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Background / Objectives

While the colposcopic terminology of the International Federation of Cervical Pathology and Colposcopy (IFCPC) is recommended to be used worldwide (1), in 2017, the Society for Lower Genital Tract Disorders (ASCCP) published “a terminology for colposcopic practice,”(2).

The 2011 IFCPC terminology most important issue was the determination of the three types of the transformation zone (TZ). In addition, the terms “satisfactory colposcopy” and “unsatisfactory colposcopy” were replaced with three variables characterizing the cervix: 1. adequate or inadequate, with the reason given; 2. squamocolumnar junction (SCJ) visibility; and 3. TZ types. One of the changes the 2017 ASCCP made was to drop the use of the TZ types and the cervical excision types that are based on the TZ types. Instead of using “adequacy” and “visibility,” the ASCCP terminology uses “visibility” for both parameters.

In addition, instead of using minor grade lesions and major grade lesions, the ASCCP now introduced the terms “low-grade” and “high-grade” changes. These new terms might create confusion. The patient may end up with a diagnosis of “low-grade” lesion in colposcopy and “high grade” in the pathology report.

Results

The concerns regarding the 2017 ASCCP terminology were presented in the Journal of Lower Genital Tract Disease. The authors of the 2017 ASCCP terminology responded, defending the 2017 ASCCP terminology (3).

Conclusion

The authors of the 2017 ASCCP terminology defended their terminology (3), raisng, among other issues: "The US health-care system differs from the rest of the world, and colposcopy training and practice differs markedly compared with other countries. In the United States, there is a shortage of colposcopy providers in many states and rural areas, and those who perform colposcopy do not have the benefit of a large referral base with high numbers of colposcopy examinations on an annual basis. The goal of the Colposcopy Standards effort was to improve colposcopy practice in all US settings. Therefore, the ASCCP has set forth a terminology that has a greater chance at being adopted by a wide range of US providers."

References

Using the 2017 ASCCP terminology for colposcopic practice in the USA is unsatisfactory and confusing. But the main concern is the shift of a significant national colposcopic society such as the ASCCP away from the international consensus reached by the IFCPC. The newly proposed ASCCP terminology for colposcopic practice stands against the IFCPC's continued efforts to unify terminology and is not based on solid evidence.

References

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00575

Risk of high grade CIN (CIN2+) in women with persistent high risk HPV genotypes and negative cytology

21. Colposcopy

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Background / Objectives

To measure the risk of HG-CIN in women referred with persistent hr-HPV infection and negative cytology at 12 or 24 months post first positive hr-HPV/cytology negative test.

Results

Service evaluation between 1/6/14 and 31/7/18 of all women referred to a single colposcopy clinic within an organised screening programme evaluating hr-HPV primary screening. HPV genotyping was performed by Roche Cobas (HPV16,HPV18+ HPV O (31,33,35,39,45,51,52,56, 58,66,68)

Conclusion

91,564 women underwent hr-HPV primary screening. 2270 women (year 1 = 270; year 2 = 681, year 3 = 739, year 4 = 580 (10months) were referred. Single infections with HPV 16 were found in 27%, HPV 18 7% and HPV O genotypes in 53%. Multiple infections were present in 13 % of cases. The risk of HG-CIN was 1 in 8.5 for HPV 16, 1 in 17 for HPV 18 and 1 in 20 for HPV O. The risk increased to 1in 8.5 for HPV 16 plus any HPV genotype. In risk of LG-CIN was low, 1 in 30, for all HPV genotypes. The overall PPV for HG-CIN colposcopic impression was 40.6%, HPV16+any 59.0%, HPV O 38.4%

References

hr-HPV testing is more sensitive than cytology however over 66% of women with a persistent hr-HPV infection will have negative reflex cytology. Women who have persistent hr-HPV infection with negative cytology are at risk of having HG-CIN, between 11 and 12% of women with HPV 16 falling to 5% for women with HPV O infections. This category of referral to colposcopy represents a significant increase in

referrals to colposcopy. The low prevalence of disease in such a large group of extra referrals will pose problems for the diagnostic performance of colposcopy.

CS2. High grade Vulvar HSIL (VIN) versus Differentiated VIN: clinical, molecular, virological and therapeutic differences

00178

The new ISSVD terminology of VIN

24. Vulvar diseases and neoplasia

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Background / Objectives

The terminology for vulvar intraepithelial lesions was repeatedly discussed lately, as the introduction of the Lower Anogenital Squamous Terminology (LAST) in 2012 raised 2 concerns in relation to vulvar lesions: firstly, the absence of reference to “differentiated vulvar intraepithelial neoplasia” (differentiated VIN) could lead to its being overlooked by health care providers, despite its malignant potential. Secondly, including the term “low-grade squamous intraepithelial lesion” (LSIL) in LAST recreated the potential for overdiagnosis and overtreatment for benign, self-limiting lesions.

Results

The International Society for the Study of Vulvovaginal Disease (ISSVD) discussed the optional proposals of terminology .

Conclusion

TABLE: The 2015 ISSVD Terminology of Vulvar SILs (1)
• LSIL of the vulva (vulvar LSIL, flat condyloma, or HPVeffect)
• HSIL of the vulva (vulvar HSIL, VIN usual type)
• DVIN

Legend: SIL indicates squamous intraepithelial lesion;
LSIL, low-grade SIL;
HPV, human papillomavirus;
HSIL, high-grade SIL;
VIN, vulvar intraepithelial neoplasia;
DVIN, differentiated-type VIN.

References

The new terminology includes all types of vulvar SILs, it provides a solution to the concerns in relation to the application of LAST to vulvar lesion, and it is in accordance with the World Health Organization classification as well as the LAST, creating unity among clinicians and pathologists.

References

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00568

HPV VACCINES TO PREVENT VIN

24. Vulvar diseases and neoplasia

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Background / Objectives

Vulvar intraepithelial neoplasia (VIN) is an increasingly common premalignant condition. There is no screening test for VIN, and early detection is limited to visual assessment, with biopsy and histopathology. This often leads to missed or delayed diagnosis. High index of suspicion is needed for vulvar lesions not responding to usual therapy. ISSVD recommends the terms vulvar LSIL (low grade squamous intraepithelial lesion) and vulvar HSIL (high grade squamous intraepithelial lesions) to replace the VIN terminology. Treatment of VIN is often mutilating and recurrencies are common, particularly with multifocal disease. Women with VIN often have concurrent cervical or vaginal lesions. A substantial number of untreated vulvar HSIL can progress to cancer.

Results

High risk HPV infection is the most important risk factor for VIN. One recent study of 8798 women aged 15-26, followed for 4 years, demonstrated at least one of 14 oncogenic HPV types in 72% of vulvar LSIL and in 91% of HSIL. Lesions with multiple HPV genotypes were common (1). Thus, there are high hopes for primary prevention of vulvar LSIL and HSIL disease burden by HPV vaccination. Large global HPV vaccination trials have demonstrated that the prophylactic HPV vaccines are highly effective in the prevention of high grade VIN. For instance, the FUTURE trial of the quadrivalent HPV vaccine demonstrated 77% efficacy against high grade VIN in the HPV naive population, and 51% efficacy in the intention-to-treat population. It is more than likely that this translates to cancer prevention in real life. HPV vaccination programs have already been implemented in multiple countries. Long-term follow-up based on cancer registries has demonstrated high vaccine efficacy in the prevention of HPV related cancers (2).

References

Unfortunately populations with the highest incidence of disease still remain largely unvaccinated. Rapid roll-out of the vaccines in low-income countries is needed to

narrow present inequalities in anogenital cancer burden and prevention. Elimination of high risk HPV types by vaccination is possible by 80% gender-neutral coverage if high vaccine efficacy is maintained (3-5).

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CS3. Revisiting the objectives: risk markers for cervical cancers (excluding HPV triage)

00540

VALHUDES: a protocol for VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples

10. Self-sampling

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Background / Objectives

Background

Systematic reviews have concluded that hrHPV DNA testing using target-amplification tests is as accurate on vaginal self-samples as on clinician-taken specimens for the detection of cervical precancer. However, insufficient evidence is available for specific HPV assay/self-sample device combinations.

Objectives

The VALHUDES protocol is designed as a diagnostic test accuracy study that aims to compare the clinical sensitivity and specificity of particular hrHPV assay(s) on

vaginal self-samples and first-void-urine, collected in agreement with standardized protocols, with hrHPV testing on matched clinician-taken samples.

Results

Five hundred enrolled women referred to a colposcopy clinic are invited to collect a first-void urine sample and one or more vaginal self-samples with particular devices before collection of a cervical sample by a clinician. Sample sets are subsequently analysed in a laboratory accredited for HPV testing. Disease verification for all enrolled patients is provided by colposcopy combined with histological assessment of biopsies.

Conclusion

A first VALHUDES study has started in Belgium in December 2017 with enrolment from four colposcopy centres. The following assays are foreseen to be evaluated: RealTime High Risk HPV assay (Abbott), cobas-4800 and -6800 (Roche), Onclarity (BD), Xpert HPV (Cepheid) and Anyplex II HPV HR (Seegene).

References

Given empirical evidence that the relative accuracy of HPV-testing on self- vs clinician-samples is robust across clinical settings, the VALHUDES protocol offers a framework for validation of HPV assay/self-sample device combinations that can be translated to a primary screening setting.

00590

E6-E7 EXPRESSION AS MARKERS FOR TANSFORMATION AND PROGRESSION

20. Diagnostic procedures / management

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Background / Objectives

Transformed cervical epithelial cells are dependent on continued expression of HPV oncoproteins E6 and E7. Early seminal experiments knocking down oncoprotein expression in cervical cancer cell lines showed the immediate induction of apoptosis or senescence. Continued oncoprotein expression during carcinogenesis is also accompanied by a marked upregulation of expression. Thus, the barely detectable expression in transient HPV infection and low grade dysplasia is upregulated during carcinogenic progression and increased in high-grade dysplasia and invasive cancer. Responsible mechanisms are selection of more transformed cells prevailing during the steps of disease progression. Upregulation of expression can be observed by loss of E2 repressor expression e.g. by E2 gene deletion after genome integration or promoter methylation, E6/E7 promoter methylation leading to inhibition of E2 binding and thus derepression, or HPV copy number amplification resulting in more transcribed genes.

These molecular events result in enhanced E6 and E7 transcription and stronger carcinogenic activity of the gene products. Molecular tests quantifying oncogene expression, mRNA splicing, and detection of the oncoproteins can be used to detect progressive lesions and discriminate potentially from non-progressing lesions with a higher potential of regression. Prognostic information could be obtaind on lesions with the high-grade molecular expression pattern of E6/E7 but still low-grade morphologic appearance.

Using E6 and E7 as specific biomarkers for cervical cancer risk has the advantage of using targets directly associated with the viral transfomation process and the cellular dependence on their expression.

Results

(Invited talk: Revisiting the objectives: risk markers for cervical cancer (excluding HPV triage))

CS4. Oncological safety and Reproductive morbidity after treatment for CIN

00631

National Data from England & Wales on Invasive cervical cancer incidence post-treatment and Risk of preterm birth

07. Immunotherapy - Immuno-oncology - New treatments

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Background / Objectives

We know that even after treatment for cervical disease risk of invasive cervical cancer remains. We also know that women who are treated for cervical disease are at higher risk of a subsequent preterm birth compared to the general population. Should clinicians be worried about this? Is the absolute risk big enough to elicit a change in practice? Using data from the English audit of invasive cervical cancers and from the PaCT study (risk of preterm delivery after treatment for cervical disease) I will show what these risks mean in absolute terms for women diagnosed with high grade cervical intraepithelial neoplasia.

Methods

In session CS4 - Oncological safety and reproductive morbidity after treatment for CIN

Conclusion

-

00511

The impact of excisional treatment on the vaginal microbiota and innate cervical immune system

17. Microbiome

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Background / Objectives

The innate immune system, along with the vaginal microbiota (VMB) provide defence against infections including HPV. Lactobacillus spp. depletion has been associated with CIN and as pre-term birth (PTB). Treatment with conisation increase the risk of preterm birth; the mechanism remains unclear. We aimed to investigate the impact of excisional treatment for CIN on VMB composition, antimicrobial peptides (AMPs) and pro-inflammatory cytokine expression.

Results

Population: Non-pregnant, premenopausal women attending the colposcopy clinic for a) excisional treatment of histologically-proven CIN (treatment group) (n=103) and b) healthy women with normal cytology and colposcopy (n=40).

Analysis: Vaginal swabs collected before treatment, and at six-month follow-up and used for 16s rRNA bacterial sequencing and enzyme-linked immunosobent assay (ELISA) to quantify AMP and cytokine levels.

Conclusion

Women with CIN had higher diversity than normal controls, while excisional treatment did not significantly alter the CSTs. The proinflammatory cytokines IL-1b and IL-8 were both significantly elevated before treatment compared to normal controls and remained higher despite excision of the disease. Levels of two AMPs; Human Beta Defensin-1 (hBD-1) and Secretory Leucocyte Protease Inhibitor (SLPI) were significantly lower after treatment compared to controls.

References

Women after treatment continue to have a high-diversity, Lactobacillus spp. deplete VMB, higher levels of proinflammatory cytokines and lower AMP levels. This may result in inferior protection from infectious agents leading to increased risk of preterm birth in a subsequent pregnancy and higher risk of disease recurrence as opposed to the general population.

00513

The role of the vaginal microbiota in the progression or regression of untreated CIN2 lesions

17. Microbiome

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Background / Objectives

The vaginal microbiota (VMB) and, in particular, a high-diversity, Lactobacillus spp. deplete community state type (CST) IV has been associated with increased acquisition and persistence of HPV infection, and increased CIN disease grade. The impact of the VMB in the natural history of CIN in serial samples has not been evaluated.

We aimed to assess whether the VMB composition impacts on the chances of progression or regression in women with untreated CIN2 lesions.

Results

Population: Non-pregnant, premenopausal women attending a colposcopy clinic with histologically-proven CIN2 in San Franscisco, USA.

Interventions: Bacterial DNA was extracted from serially collected liquid-based cytology samples and sequenced using the Illumina MiSeq platform.

Analysis: Heirarchical clustering of sequence data was used to examine bacterial species classification data.

Conclusion

Of the 87 women included in the cohort, 44.7% had regressed by 12 months (39/87), 66.7% (58/87) by 24 months, and 73.5% (64/87) by 36 months. CST IV was associated with higher rates of disease persistence and slower disease regression compared to Lactobacillus spp.-dominant CST's. At 24 months, women who regressed were significantly more likely to have a CST I microbiota, and less likely to

have CST IV compared to those who persisted (p=0.0001, one-way ANOVA). At 36 months CST IV was also significantly associated with persistence compared to regression (p=0.0004, one-way ANOVA). Anaerobic species including Megasphaera (p=0.011), Allisonella (p=0.022), Prevotella timonensis (p=0.026) and Gardnerella (p=0.035) were significantly more abundant in women with persistent disease at 12 months compared to those who regressed.

References

Our findings suggest paucity of Lactobacillus spp. may be associated with CIN2 persistence and slower regression. Further research in the impact of VMB on the natural history of CIN may help us identify a VMB composition and microbiological markers that may signify women at high risk of progression that require treatment and the development of new treatment targets.

CS5. Which populations should be assessed for anal cancer and/or precancer screening?

00596

HIV-negative MSM

09. HPV screening

G. Dsouza

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Background / Objectives

This talk reviews anal cancer risk among HIV-negative MSM including epidemiology, trends, prevalence of HPV infection, pre-cancer, and dysplasia. Utility of screening in this population will be discussed.

Results

In session: CS7. Which populations should be assessed for anal cancer and/or precancer screening?

References

NA

WACC1. Understanding public attitudes to improve education

00211

Survey on Attitude of HPV Vaccination for Cervical Cancer Prevention Among Female Migrant Population in Shenzhen area

05. HPV prophylactic vaccines

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Background / Objectives

To investigate the attitude and intention of female migrant population for human papillomavirus (HPV) vaccination and the associated factors in Shenzhen area.

Results

Totally 969 female migrant residents were recruited in community health centers of 10 districts by a convenience sampling method. The information on demographic characteristics, sex behavior, and attitude towards HPV vaccination. The logistic regression model was applied to analyze possible associated factors.

Conclusion

The average age of all participants was 35.34±8.21 years old. Despite awareness of HPV (29.2%) were low, willingness to be vaccinated against HPV (56.6%) was relatively high in 969 female migrant residents. The main reasons for unwillingness of vaccination were worrying the safety of vaccine (34.7%), HPV vaccination not being widely accepted (17.8%), the high price of vaccine (11.4%), not trusting the effectiveness of vaccine (9.7%), not considering themselves at risk of cervical cancer (9.7%), and no effect of vaccination when having sexual behaviors (8.3%). Women who were middle age (OR:1.464 and 95%CI:1.053~2.037), Han nationality (OR:1.674 and 95%CI:1.010~2.774), having senior high school degree and above (OR:1.945 and 95%CI:1.201~3.150), and having commercial or other health insurances (OR:1.594 and 95%CI:1.104~2.301) were associated with higher willingness of HPV vaccination.

References

HPV awareness was low among female migrant residents, but most of them were willing to be vaccinated. Among migrant residents, females who were at early ages,

non-Han nationality, having low-levels of education, and without health insurances should be transfused appropriate knowledge of HPV and cervical cancer.

00172

PSYCHOSEXUAL IMPLICATIONS OF ROUTINE PRIMARY HUMAN PAPILLOMAVIRUS TESTING IN THE ENGLISH CERVICAL SCREENING PROGRAMME

08. HPV testing

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Background / Objectives

The cervical screening programme in England will implement primary HPV testing from 2019. This will change the cervical screening results women receive. Previous research suggests that abnormal cytology screening results can have a negative impact on psychosexual outcomes such as frequency, interest and satisfaction with sex; however the impact of primary HPV testing on these outcomes is unclear. This study aimed to explore the psychosexual impact of primary HPV testing among women with different screening results.

Results

Women were recruited from five sites in England where primary HPV testing is being piloted. They completed a postal survey approximately two weeks after receiving their screening results, as part of the PIPS study (1). Psychosexual burden was assessed using PEAPS-Q and compared across six groups of women with different HPV and cytology results using ANCOVA. Analysis included women with complete data (n=908 out of 1142).

Conclusion

Women who were HPV negative and those who had a normal cytology result with no HPV test had mean psychosexual burden scores of 1.36 (SE=0.12) and 1.31 (SE=0.11) respectively (out of a possible 6, where higher score indicates greater burden). These groups did not differ (p=1.00) and were combined to form a control group. Compared to this control group, women who were HPV+ had higher psychosexual burden ($\overline{X}$=2.32, SE=0.11 for HPV+ with normal cytology; $\overline{X}$=2.32, SE=0.12 for HPV+ with abnormal cytology and $\overline{X}$=2.26, SE=0.12 for persistent HPV with normal cytology at 12-months). Previously HPV+ women who had cleared the

infection at 12 month follow-up also scored significantly higher than controls ($\bar{X}$=1.77, SE=0.15).

References

Testing positive for HPV regardless of cytology result appears to have a statistically significant adverse impact on psychosexual functioning. Psychosexual impact did not differ between women who tested HPV negative and those not tested for HPV, suggesting that HPV testing itself does not impose a psychosexual burden. While the results suggest that the psychosexual impact is modest (an increase of ~1 on a 6-point scale), it is important to understand and minimise the psychosexual burden of testing positive for HPV to ensure this does not cause undue concern among women, have an adverse effect on their relationships or influence future screening re-attendance.

References

(1) McBride E, Marlow L, Forster AS, Moss S, Myles J, Kitchener H, Patnick J, Waller J. Psychological Impact of Primary Screening (PIPS) for HPV: a protocol for a cross-sectional evaluation within the NHS cervical screening programme. BMJ Open. 2016 Dec 23;6(12):e014356.

00149

PSYCHOLOGICAL IMPLICATIONS OF ROUTINE HPV PRIMARY TESTING IN CERVICAL SCREENING: A CROSS-SECTIONAL SURVEY ASSESSING ANXIETY AND DISTRESS

09. HPV screening

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Department of Behavioural Science and Health, UCL (United kingdom)

Background / Objectives

The psychological impact of integrating routine communication of HPV status into cervical screening is unknown, but previous research suggests some women will experience adverse psychological responses to testing HPV positive. Ahead of the planned implementation of HPV primary screening across England in 2019, we examined differences in anxiety and distress between women receiving different test results at five sites where HPV primary screening is being piloted.

Results

Women (n=1,132) completed a postal survey approximately 2 weeks after receiving their screening results, as part of the PIPS study (1). Anxiety, distress, reaction to results (concern and reassurance), worry about developing cervical cancer and perceived risk of cervical cancer were compared across six groups with different HPV and cytology results.

Conclusion

Anxiety was higher in women with any HPV+ result compared with women testing HPV- (Welch's $F(5, 359)=9.35, p<.001$) and was similar across HPV+ groups regardless of whether the cytology result was normal or abnormal ($p>.05$). Distress was higher in women who tested HPV+ with abnormal cytology, and in those receiving an HPV+ with normal cytology result for the first time (Welch's $F(5, 394)=3.41, p<.001$). Worry and concern were higher, and reassurance lower, in HPV+ groups ($p<.001$).

References

Testing positive for HPV, regardless of cytology result, appears to raise anxiety, worry and concern. Distress was slightly elevated in some HPV positive groups,

indicating that for some women an HPV diagnosis can disrupt everyday functioning. Rigorous behavioural science input is needed to inform the wording of test result letters and information materials to minimise unnecessary anxiety and mitigate possible adverse effects on screening re-attendance rates.

References

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00415

Unanswered questions among women participating in the English primary HPV testing pilot: A content analysis

09. HPV screening

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Background / Objectives

HPV primary testing is being implemented in several countries. This means changes to the results that women will receive. It is important to ensure that the information provided adresseses information needs. In this study we asked women participating in primary HPV testing if they had any unanswered questions. Our objective was to identify the content and prevalence of topics raised.

Results

Women participating in the primary HPV testing pilot in England were sent a questionnaire after their results. Women represented five results groups: HPV negative, HPV positive with normal or abnormal cytology, persistent HPV or HPV cleared (at 12-months). Towards the end of the questionnaire women were asked “Do you have any unanswered questions about cervical screening or HPV testing”. A space was also provided for “other comments”. Women’s verbatim responses constituted the data for this Content Analysis.

Conclusion

A third of women recorded a verbatim question or comment (335/932). HPV positive and HPV cleared women were more likely to record a response than HPV negative women (34-45% versus 23%). General lack of understanding or specific questions about the cause and epidemiology of HPV were raised (38%). Women commonly referred to their results (40%), clarifying the meaning, expressing emotional responses and concern about sexual relationships, as well as questioning the accuracy of HPV testing. HPV positive and HPV cleared women were the most likely to raise this theme (36%-50% compared with 17% of HPV negative women). Comments and questions about the purpose of HPV primary screening, including the timing between tests and why cytology was not always completed, were also raised and this theme was most common among HPV negative women (38% compared with 13-22% of HPV positive and HPV cleared women). Other themes included

clarifying risk of cervical cancer (11%), information seeking (19%) and questions about implications for fertility, treating/clearing HPV and testing male partners (16%).

References

Some women invited for HPV-based screening continue to have a wide range of unanswered questions. Detail about the epidemiology of HPV, why the cervical screening procedure is changing and the meaning and implications of different results, particularly for sexual relationships, should be provided in information materials accompanying results. Some results groups may benefit from additional tailored information.

00112

INCREASING UPTAKE OF HPV VACCINATION USING AN ADOLESCENT INCENTIVE INTERVENTION: A CLUSTER RANDOMISED FEASIBILITY TRIAL

33. Advocacy, acceptability and psychology

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Background / Objectives

Uptake of human papillomavirus (HPV) vaccine is suboptimal in England among girls from ethnic minority backgrounds and in some geographical regions, particularly London. This variation in uptake has the potential to widen inequalities in HPV-related disease (1). As part of the school-based HPV immunisation programme, a consent form with parental signature has to be returned regardless of whether consent for vaccination is given or withheld. Lack of a signed consent form is the main reason for adolescent girls not receiving the vaccine in England. We aimed to determine the feasibility of undertaking a cluster randomised controlled trial (RCT) of incentivising consent form return to improve HPV vaccine uptake.

Results

We used an equal-allocation, two-arm cluster RCT design and invited 60 schools in London to participate. Schools agreeing to participate were randomised into one of two arms: a standard invitation or incentive intervention arm. In the incentive intervention arm 12-13 year old girls were given the chance to win a £50 shopping voucher if they returned a vaccination consent form, regardless of whether consent was provided. Data was collected on school and parent participation rates, questionnaire response rates, consent form return and vaccine uptake. We analysed the data descriptively. The trial was preregistered (ISRCTN72136061) and protocol published (2).

Conclusion

There were six schools that completed the trial. Only around 3% of parents opted out. Around 70% of girls returned a questionnaire and 17% of parents returned a questionnaire. In the intervention arm, 87% of girls returned a consent form compared to 67% in the standard invitation arm. The proportion of girls whose

parents gave consent for vaccination was higher in the intervention arm (76%) than the standard invitation arm (61%). Preliminary data suggested that the incentive may work by helping girls to remember to return their consent form. Furthermore, girls in the intervention arm were more likely to give their parents the consent form to sign on the day that they received it from school (70%) compared to girls in the standard invitation arm (58%).

References

A RCT of an incentive intervention is feasible. The intervention may improve vaccination uptake but a fully-powered RCT is required. This incentive intervention has the potential to substantially improve HPV vaccination uptake, which should reduce HPV-related cancer incidence, with minimal work from immunisation providers.

References

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00035

WHAT UK HEALTHCARE PRACTITIONERS KNOW ABOUT HPV AND IMPLICATIONS FOR TRAINING

34. Health education

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Background / Objectives

Human papillomavirus (HPV) is a common sexually transmitted infection implicated in 5% of cancers worldwide. Since 2008 there has been a vaccine available in the UK that is administered to girls aged 12-13 (11-13 in Scotland). It is not currently available to boys, although considerable lobbying means that this is likely to change in the future. HPV testing is also being incorporated into the NHS cervical screening programme to replace cytology as the primary screening method. The current research evaluates UK-wide knowledge about HPV and its implications for both males and females, the vaccine and the changes to the screening programme in healthcare practitioners (HCP) who provide HPV vaccination, cervical screening and colposcopy services or related advice.

Results

Participants (N=643) were recruited by Jo's Cervical Cancer Trust using their health care professional networks and completed an online survey covering demographics, level of experience, HPV knowledge, HPV triage, Test of Cure (TOC) and primary HPV testing knowledge, HPV vaccine knowledge, attitudes towards the HPV vaccine and self-perceived adequacy of HPV knowledge. Data collection took place between March and April 2018.

Conclusion

Most participants were female (99.2%), nurses in GP practice (80.6%) and from England (70.8%) or Scotland (21.4%). Experience of smear taking ranged from 1 month to 40 years and 92.4% had undertaken cervical sample taker update training. Participants had a generally good understanding of HPV (mean score of 20.1 out of

23) and the vaccination (mean score of 5.9 out of 7) but there were crucial gaps in knowledge around the impact of HPV on men as well as gaps in detailed knowledge of the NHS HPV testing processes. For example, only 64.6% correctly identified that HPV can cause oral cancer. In both univariate and multivariate analyses, years since HPV training was associated with Triage and TOC knowledge score and vaccine knowledge score, where those with more recent training were more likely to have a higher knowledge score. Furthermore, nurses and doctors in colposcopy clinics had much greater odds of having higher knowledge across all domains than other roles. 76.2% of participants felt adequately informed about HPV and 36.4% made suggestions for improvements in training, many of which centred around online training.

References

Significant stigma and distress have been reported to be associated with cervical screening and HPV testing, it is vital healthcare practitioners are well-informed in order to alleviate these issues. Our results suggest that additional training is needed to ensure HCPs are equipped to deal with the changing landscape of HPV screening and vaccination in the UK.

00340

Awareness of risk factors for cervical cancer among screening non-participants in Great Britain

34. Health education

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Background / Objectives

Identifying gaps in cervical cancer knowledge will highlight important content for inclusion in screening information materials and public education campaigns. This study explored knowledge of cervical cancer risk factors among cervical screening non-participants in Great Britain and variation across sub-groups of non-participants (as classified using the Precaution Adoption Process Model, PAPM)(Weinstein, 1988).

Results

A cross-sectional survey of women eligible for cervical screening (i.e. aged 25-64 years living in Great Britain) was used to identify cervical screening non-participants. Women completed self-report questions about their past screening attendance and future intentions, and were classified into five different groups of screening non-participants in line with the PAPM (unaware of screening, unengaged with screening, undecided, decided not to be screened, intending to get screened). Women were presented with eight established risk factors and asked whether they agreed that this could increase a woman's risk of cervical cancer. Those who agreed were considered to be 'aware' of that risk factor.

Conclusion

Overall 819 screening non-participants took part in the study and responded to the risk factor questions. Awareness of cervical cancer risk factors was low; the mean number of risk factors correctly identified was 3.43 (SD = 2.54). The most commonly known risk factors were 'not going for regular smear (Pap) tests' (56% aware) and 'having many sexual partners' (46%). The least commonly known risk factors were 'long term use of the contraceptive pill' (29%) and 'starting to have sex at a young age' (35%). Only 39% were aware that infection with HPV was a risk factor for cervical cancer. Women who intended to be screened were more like to identify 'not going for regular smear tests' as a risk factor for cervical cancer than the other non-

participant groups (66% compared with 38-49%). Awareness of the other risk factors did not differ across non-participant groups.

References

This study suggests that all types of screening non-participants are inadequately informed about cervical cancer risk factors, including not going for regular cervical screening and infection with HPV. This information should be highlighted in screening information materials and public education campaigns to facilitate informed choice about screening.

References

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00404

LEVERAGING ELEARNING, EXPERIENCES FROM A COURSE ENTITLED: HUMAN PAPILLOMA VIRUS - FROM MOLECULAR BIOLOGY TO GLOBAL HEALTH

34. Health education

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Background / Objectives

Higher education is increasingly moving towards online platforms to deliver coursework. When delivered in an open access manner, online platforms have the potential to facilitate the spread of evidence-based strategies and encourage cross-national information sharing.

Results

A 1-week 1.5HEC eLearning course was designed, marketed, and then delivered in early spring of 2018. The target group was to PhD students, post-docs and professionals from health care, universities and biomedicine with an interest in Human Papilloma Virus and cancer research. Topics covered by the course included: HPV infection and the burden of HPV-associated diseases, methods for detection of HPV and the bioinformatics methods for HPV classification, best practices for organized cervical screening, assessment of internationally standardized quality indicators of cervical screening, and validation of results from screening and vaccination and their implications on the cancer burdens. Students watched video lectures, completed written assignments, and participated in real-time online chats.

Conclusion

In total, 48 students from 18 countries completed the course. Given that the coursework is now posted as open access lectures, the material is transparent and open for international discussion (available on the Nordice eScience Booc YouTube channel: https://www.youtube.com/channel/UCIuceVSkXrx3M4dgcQsoqHQ/videos).

References

The course evaluation highlighted the desire for more courses in an eLearning format, as it allowed for participation across the globe.

00605

Effect of an educational intervention on HPV knowledge and attitudes towards HPV and its vaccines among junior middle school students in mainland China

34. Health education

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Background / Objectives

HPV vaccine was not accessible in mainland China until May 2017 due to government regulations and few girls in junior middle schools have never heard of HPV and HPV vaccines. Little is known about the knowledge and attitudes towards HPV and its vaccines among adolescents in mainland China. Also, limited information was available on how to improve their knowledge and willingness towards HPV and its vaccines to ensure a successful vaccination program in the future.

Results

This was a school-based interventional follow-up study. One urban and one rural junior middle school were selected by convenience sampling from the representative city in seven geographic regions. At baseline, one of the grade one class students were randomly selected as controls and another one class were interventions. A set of self-administered questionnaires on HPV and its vaccines were completed by both groups at baseline. After that, only the intervention group received a PPT-oriented health education and finished the post-education questionnaires. One year later, both groups completed the same questionnaires as the post-education questionnaire.

Conclusion

Of all, 5184 students have finished the pre-intervention questionnaires, 2483 were from the control group and 2701 were from the intervention group. Among them, only 12.5% had ever heard of HPV and 15.6% had heard of the HPV vaccine. However, 61.0% of students showed their willingness to be vaccinated even before any

intervention. Seven variables were found to be associated with the willingness to be vaccinated at baseline. Immediately after the intervention, 90.6% of students were willing to vaccinate themselves. After one year, the effectiveness of intervention remained but decreased. Compared with the control group, the intervention group was more aware of cervical cancer, HPV and its vaccines ($P<0.05$). However, the level of HPV knowledge and willingness to be vaccinated had significantly decreased compared with that one year ago immediately after the intervention ($P<0.001$).

References

The baseline level of knowledge on HPV, its vaccines, and cervical cancer is extremely low among junior middle school students in mainland China. However, the willingness to be vaccinated seems positive. School-based health education is effective and appropriate in increasing the awareness and willingness towards HPV and its vaccines. Regular health education on HPV and cervical cancer prevention at a shorter interval should be guaranteed to ensure continuous effectiveness.

00228

SENSE AND SENSIBILITY: SOURCES OF INFORMATION IN MOTHERS WHO REJECT HPV-VACCINATION OF THEIR ADOLESCENT DAUGHTERS

36. Public health

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Background / Objectives

Vaccination against human papillomavirus (HPV) has been part of the free-of-charge Danish Childhood Vaccination Programme (CVP) for 12-year-old girls since 2009 and initially yielded a relatively high uptake (>90%) until an intense public debate on alleged side effects broke out in 2015, dramatically lowering coverage rates to below 25% at the time.

As the rest of the CVP still had coverage rates close to 90%, a significant difference in decision-making between vaccinations was suspected. This study aimed to describe the sources of information and socioeconomic predictors for mothers who rejected HPV-vaccination of their adolescent daughters.

Results

In 2018, we invited 6,814 mothers of daughters born in 2003 living in the Central Denmark Region to participate in an online survey. The survey examined, among other things, sources of information and factors of value during decision-making. A cross-sectional analysis of register and survey data from 3,581 respondents was conducted. Data on socioeconomic factors was retrieved from Statistics Denmark.

Differences in socioeconomic factors between both respondents and non-respondents and those who accepted and declined vaccination were determined. Associations between vaccination status and information sources, family members involved in decision-making, and factors of value were assessed using logistic regression.

Conclusion

Statistical analyses are on-going, but preliminary results indicate that information sources are of less importance than the impression they leave behind. We find strong evidence that women who seek guidance from their general practitioner (GP) and are recommended vaccination are more likely to vaccinate their daughters compared to women who are not, while mothers who are primarily informed through social media and value media are more likely to decline vaccination than women who do not. We will be able to present the final results at the conference.

References

This study, the biggest of its kind, provides evidence that mothers are liable to make health-care decisions based on sensibility instead of sense.

00366

Do new media channels reach the target screening audience. A snapshot of social media campaigns in Norway for cervical cancer screening participation.

36. Public health

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Background / Objectives

High attendance rate in screening programs is important to achieve high disease preventive effect. In the last ten years, there has been a decline in the participation rate. We explain different strategies to reach women through social media in correlation with cervical cancer screening participation.

Results

Social media, television, radio and newspapers have been used to increase awareness of cervical cancer screening in the general population. The Facebook public page, “Kreftsjekken” (“Cancer check”), releasing information specifically tailored to selected groups has been ongoing since 2014 (1). Another national campaign, #sjekkdeg (“get checked”) was launched in 2015 by a young blogger diagnosed with cervical cancer. Personal reminders, either through letters or electronically notify women when it is time to take a screening test. These have been sent out since the start of the program. The number of registered screening tests, and 3.5-year screening coverage by age, were calculated from the national screening databases at the Cancer Registry of Norway (2).

Conclusion

Different strategies is in use to increase the awareness of the importance of regular screening attendance among the whole target group of the Norwegian Cervical Cancer Screening Programme. The strategies are not able to be evaluated for causality. However, overall cervical cancer screening coverage has increased from 65% to 70% in 2013-2017. This is in line with the increasing trend of social media use in Norway, in particular Facebook, which is the most popular among all the social media platforms.
In 2017, posts at “Kreftsjekken” directed specifically to women living in the two

counties with the lowest coverage, resulted in comments in the local newspapers and on radio. In these two counties, the coverage increased with more than 4% among younger women aged 25-34, compared to 2% on average for the whole of Norway. For the older women, aged 34-69, approximately 1% increase was observed, similar to the rest of the country. After the initiation of “Sjekkdeg” In 2015, targeting mainly the youngest women, the coverage has increased in the age group 25-29 with 9%. For the whole target population the increase has been 4%.
About 50% (2018) of the women receive their reminders electronically, and this group has a higher participation rate by 13%.

References

Increasing knowledge about preventing cervical cancer is a continuing process. Because Norway is a country with a scattered population, lack of availability must also be taken into consideration. The use of social media platforms must be monitored and updated as its use is increasing across all age groups.

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00375

IMMUNIZATION CAMPAIGNS AGAINST HPV: THE RESULTS OF A SURVEY TO REGIONAL AND LOCAL HEALTH UNITS REPRESENTATIVES

36. Public health

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Background / Objectives

Before the implementation of the National Immunization Plan 2017-20191, different vaccination strategies against HPV were adopted among Italian regions since 2008. The aim of the study was assessing the immunization campaigns and obtained results by some Italian regions that introduced the universal and/or at risk subjects immunization strategies before the national recommendations.

Results

From November 2017 to March 2018, regional and Local Health Units (LHUs) representatives were invited to complete an online survey including 54 questions evaluating immunization policies, obtained results in different targets, communication and education strategies and organisational characteristics of vaccination centres. An overall descriptive analysis was conducted. Since observed vaccine coverages (VC) obtained in females 2002-2004 birth cohorts were lower than fixed objectives, variables related to VC higher than the national mean were evaluated.

Conclusion

Twenty-six LHUs belonging to the 4 Italian regions participating to the study answered the online questionnaire. The 88.4% of LHUs introduced universal immunization strategy in 2015. The most represented invite vaccination system was letter addressed to parents by LHUs (96.2% of cases). In 76% of cases the vaccine appointment was included in the invitation letter and this practice is significantly related to VC in 2003 female birth cohort ($p=0.03$) higher than the national mean. The 80.8% of LHUs planned reserved HPV vaccine sessions. Only 69.2% and 61.5% of LHUs recalled subjects who misses the first and the second dose appointments, respectively, even though this procedure was significantly related to higher VC in all female birth cohorts ($p<0.05$). The 80.8% of LHUs planned the administration of the second dose during the first appointment. Among strategies targeting at risk population, only 26.9% LHUs had implemented a network system to identify and invite them to counselling. Among communication strategies, the informative material distributed at immunizations centers was translated in other languages than Italian only in 19.2% of cases, a telephonic HPV-information service is active in 53.8% of LHUs, local media were involved in 34.6% and parents/pre-adolescents meetings were conducted in 42.3% of cases. Healthcare workers (HCWs) education about universal vaccine strategy was related to higher CV ($p<0.05$).

References

VC observed in participating LHUs are largely lower than the national objectives in all anti-HPV vaccine targets. Furthermore, organizational strategies to reach subjects at risk are suboptimal. Obtained results suggest that recall system for missed administrations and HCWs education were related to higher CV in female. Both organizational and educational strategies have to be implemented to improve the VC goals.

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00447

FEELINGS, PERCEPTIONS AND EXPERIENCE OF POINT OF CARE HPV-DNA CERVICAL SCREENING IN PAPUA NEW GUINEA

36. Public health

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Background / Objectives

Although preventable, cervical cancer is the most common female cancer in Papua New Guinea (PNG). In accordance with WHO guidelines to introduce HPV-based screening, a trial using the GeneXpert on self-collected vaginal swabs for high-risk HPV (hrHPV) screening followed by same day treatment is being undertaken in four provinces in PNG. As with any public health intervention, ensuring that the technology is acceptable to a range of stakeholders including ‘patients’ and communities is vital to its success. Acceptability for HPV-based screening is dependent on numerous factors, including sociocultural context, knowledge of the disease and screening, as well as women’s experience of care. My research will address this critical public health gap in PNG by evaluating the acceptability of point-of-care Xpert HPV testing among women, their families and other key stakeholders in PNG. This initial phase aims to explore patients’ perceptions, and experience of care of point of care cervical screening in PNG as well as what has impacted these perceptions and beliefs. Results from this phase will aim to enrich health education messages and improve the quality of services provided for a better screening experience in hopes of increasing cervical screening uptake in PNG.

Results

For this phase, 22 semi-structured interviews were conducted during the months of April and May 2018 in Mount Hagen (in Western Highlands Province) with a random sample of study participants to better understand their feelings, knowledge and perceptions of cervical cancer as well as their experience of point of care HPV-DNA testing for the first time.

Conclusion

Based on the qualitative analysis from the first field trial site, perceptions varied and were largely influenced by the patient's immediate family or the community's perceptions of and experience with cervical cancer as well as the patient's past service provision experience including their interaction with health care workers. Nevertheless, women were satisfied with their point of care cervical screening experience (including cost associated with it).

References

These valuable preliminary data will help improve service delivery in relation to HPV screening as well as provide a preview of socio-cultural factors that impact the acceptability of a novel point of care GeneXpert HPV-DNA cervical screening technology in the country.

WACC2. Communication on sexually transmitted HPV: what should the clinician and patient know?

00201

Difficulties Associated with Communicating HPV Positive Test Results to Women

08. HPV testing

E. Daley

University of South Florida College of Public Health - Tampa (United States of America)

Background / Objectives

The development and implementation of the Pap test as a cervical cancer screening mechanism in the 1940-50's lead to a remarkable decrease in mortality from this disease. Despite the Pap test being a less than effective screening tool with high rates of false negatives, decades of well-accepted screening protocol that involved an "annual exam" resulted in cervical cancer being considered a "rare" cancer.

References

Advances in scientific understanding of HPV's role in cervical cancer as well as the development and implementation of HPV testing have resulted in changes in screening guidelines that are vastly different from the well-accepted but flawed annual schedule, which often resulted in over-testing. This presentation will address some of the confusion, anxiety and mistrust among patients in reaction to the new guidelines and, using a health literacy framework, suggest approaches to improving understanding and communication among both patients and providers.

00604
From Pap to HPV: Opportunties and Challenges

09. HPV screening

M. Saraiya

Centers for Disease Control and Prevention - Atlanta (United States of America)

Background / Objectives

The shift towards sole use of HPV DNA testing to replace cytology-based testing is occurring in both high and low-income countries. This presentation will address some of the reasons for embracing primary HPV-based screening, such as a growing vaccinated population, lack of pathology-infrastructure, ability to incorporate self-collection, and cost-effective analysis. Despite this strong evidence in support of primary HPV-based screening, there are also obstacles to its implementation including cost, policy and workforce issues.

00597
Oral HPV infection

26. Oral HPV infection

G. Dsouza

JHSPH - Baltimore (United States of America)

Background / Objectives

Common questions and answers about oral HPV infection and HPV-related oropharyngeal cancer will be reviewed. Risk factors will be reviewed and discussed and levels of risk for infection and cancer reviewed. Strategies for communicating about oral HPV infection and risk will be discussed.

Results

In session: WACC2. Communication on sexually transmitted HPV: what should the clinician and patient know?

00617

Communication about Oral HPV Infection and Disease

26. Oral HPV infection

N. Osazuwa Peters

Saint Louis University School of Medicine - St. Louis (United States of America)

Background / Objectives

There has been a shift in the last three decades in the epidemiology of head and neck cancer. While the traditional risk factors for head and neck cancer (tobacco and alcohol use) remain very important, the human papillomavirus (HPV) has evolved from being a risk factor to a known cause of head and neck cancer, especially a subset in the oropharynx, or the back of the mouth and throat. This evolution could not be more challenging: HPV-associated oropharyngeal cancer has become the dominant head and neck cancer in the US and most developed nations, and in the US has become the leading HPV-associated cancer.

Results

There are however problems associated with discussing oral HPV infection from a prevention perspective, as well as the disease (HPV-positive oropharyngeal cancer) to patients and relatives. First, HPV is still regarded by many as a “woman’s business.” The lack of knowledge of HPV being gender neutral is alarming, and has not been helped by the media framing of HPV and HPV vaccine in relation to cervical cancer. Paradoxically, the disease (HPV-positive oropharyngeal cancer) is predominantly male than female. Second, HPV is sexually transmitted, and many discussions about it usually result in questions about marital distrust, fidelity issues and stigma. Third, there is prevailing and pervasive cultural shift surrounding some of the known risk factors associated with oral HPV acquisition, such as oral sex, which makes conversations about the subject difficult across ages.

References

It is important that communications about oral HPV infection and disease are clear, pointed and audience-specific. This presentation will describe some of the challenges outlined above, and proffer some suggestions to improve communication about oral HPV infection and disease.

W1. Workshop on HPV immunization

00561

REVIEW ON HPV VACCINE SAFETY

07. Immunotherapy - Immuno-oncology - New treatments

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Background / Objectives

Human papillomavirus (HPV) infection is responsible for virtually all cervical cancers, for a large share of genitourinary cancers, including vulvar, vaginal, penis, and anus cancer, as well as for oropharynx cancers – with great impact on neoplasms' burden worldwide. Despite availability of anti-HPV vaccines of proven efficacy and implementation HPV immunization programmes worldwide, HPV vaccine coverage rates remains low in target populations. Fear of adverse events following immunization has been identified as key determinant of low HPV vaccine uptake.

Results

Aim of the presentation is to comprehensively retrieve, pool and report, as well as critically appraise, the most updated available evidence on HPV vaccine safety derived by randomized controlled trials and observational studies, by vaccine type and in different target populations.

Conclusion

Accumulated safety studies and subsequent systematic reviews that include several million people have compared the risks for a wide range of health outcomes in HPV vaccinated vs. unvaccinated subjects, vs. subjects vaccinated with other vaccines or vaccine schedules. Overall, HPV vaccines have been proved not be associated with increased risk of serious adverse effects, with no evidence for a causal association between HPV vaccine and, for instance, Guillain-Barré syndrome (GBS), complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS). Although studies confirm no difference in mortality between HPV vaccinated subjects an control groups, a recent Cochrane review reported higher

number of deaths in older vaccinated women. No increased risk of miscarriage or termination has been reported in pregnant women.

References

To date no safety concerns have arisen during the HPV vaccine pre-licensure clinical trials or in post-licensure surveillance reports. Despite the extensive safety data available general population attention often focuses on spurious case reports and unsubstantiated allegations. In times where social media content boosts vaccine hesitancy it is of fundamental importance to communicate the value of HPV immunization countering misperception and wrong beliefs on its health risks.

W2. Training course for cervical cancer screening coordinators and evaluators - Screening for women difficult to reach

00129

COST-EFFECTIVENESS OF A MULTISTEP STRATEGY TO INCREASE ADHERENCE TO CERVICAL CANCER SCREENING IN PORTUGAL

08. HPV testing

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Background / Objectives

Cervical cancer screening programs are effective in reducing mortality and burden of disease, but the adherence among eligible women is often low. We aimed to investigate the cost-effectiveness of a multistep intervention to increase adherence to organized cervical cancer screening among women aged 25 to 49 years, eligible for cervical cancer screening, with a mobile phone number available.

Results

We developed a decision tree model to compare the cost-effectiveness of four competing interventions to increase adherence to cervical cancer screening: (1) a written letter (i.e., standard of care); (2) automated short message services (SMS)/phone calls; (3) automated SMS/phone calls followed by manual phone calls (MPC); (4) automated SMS/phone calls followed by MPC and face-to-face interviews. Model parameters were estimated using primary data from 1220 women enrolled in a Portuguese randomized controlled trial. Costs were calculated from the societal and provider perspective. The cost per quality-adjusted life year (QALY), over a five-year time horizon was considered the main outcome

Conclusion

The standard of care invitation was strongly dominated (i.e., more costly and less effective) by an invitation based on automated SMS/phone calls + MPC on a provider perspective and dominated by automated SMS/phone calls on a societal perspective.

From the provider perspective and below a threshold of €4286 per QALY, automated SMS/phone calls resulted in the highest level of benefit for its cost; above the threshold and below €167230 per QALY automated SMS/phone calls + MPC was the most cost-effective choice and above €167230 per QALY, automated SMS/phone calls + MPC + face-to-face interviews.

From the societal perspective, the optimal strategy of women invitation to cervical cancer was automated SMS/phone calls below a threshold of €9394 per QALY; above this threshold and below €172339 per QALY, the most cost-effective strategy was automated SMS/phone calls + MPC and above €172339 per QALY automated SMS/phone calls + MPC + face-to-face interviews.

References

Assuming a willingness-to-pay threshold of €67194 per QALY (i.e., 3 times the gross domestic product per capita in Portugal), the intervention based on automated SMS/phone calls and manual phone calls can be considered the most cost-effective strategy of inviting women to cervical cancer screening, surpassing the standard of care.

00020

HPV VAGINAL SELF-SAMPLING AMONG WOMEN NON-ADHERENT TO PAP-SMEAR IN BRAZIL

10. Self-sampling

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Background / Objectives

Cervical cancer is the fourth type of malignancy most common affecting the female population worldwide, and is attributable to persistent oncogenic HPV (Human Papillomavirus) infection. Although the public health efforts to prevent this type of cancer, part of the women are less likely to get the Pap test, which is offered cervical cancer screening in Brazil.The present study aimed to evaluate the feasibility of one cervical cancer screening strategy among women aged 30 years and above who never had a Pap test or were three or more years overdue for screening.

Results

The project was developed by Prevention Department of Barretos Cancer Hospital in partnership with the Municipal Department of Health of 18 cities that are part of the Barretos region. It was offered to the participants the possibility of self-sampled tests on their own house to detect high risk HPV (hr-HPV) which were after processed using Cobas 4800® System (Roche Diagnostics, Laval, Quebec, Canada). The test was offered to each participant by community health workers (CHW). The study was approved by the institutional review board.

Conclusion

Partial results include two hundred eighty women identified during the home visits by the CHW and invited to HPV test. A total of 268 women (96,1%) accepted the study and were tested for hr-HPV using vaginal self-sample with the Viba Brush®. The majority of these women were married/stable union (n=157, 58,6%) and 41,9% did not conclude the basic education (n=111).About having a Pap smear before, 79,9% of women who participated in this trial declared that they have at least one Pap test before the study (n=211), but at least three years ago. The mean of years overdue the Pap test were 9.4 years (SD: 5,3; 3 - 33 years). All women who have one Pap test before were asked about the preference between the self-collection versus conventional Pap-smear. 91,1% (n=191) reported to prefer self-collection test. Out of the total of 268 tests performed, 8,6% (n=23) of the woman showed at least one type of hr-HPV. 2,9% of the samples were reject for evaluation due to technical issues. All women who tested positive for at least one type of HPV were referred for colposcopy. Fifteen women already came to the outpatient clinic and received a colposcopy evaluation; 2 women refused and 6 women are waiting for a colposcopy appointment. Out of the total of 15 colposcopies, 4 (26,6%) cervical intraepithelial neoplasia grade 1 (CIN1) and 1 (6,6%) cervical intraepithelial neoplasia grade 2 (CIN2) were identified.

References

In conclusion, this trial confirms the importance of a self-sampling strategy for nonattendance women. This strategy could be a useful alternative to reach this population.

00160

HPV SELF-SAMPLING AS A TOOL TO REDUCE SOCIAL INEQUALITY IN CERVICAL CANCER SCREENING PARTICIPATION

10. Self-sampling

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Background / Objectives

Social inequality in cervical cancer screening participation exists. Self-sampling for high-risk human papillomavirus testing (HPV self-sampling) increases participation among non-participants, but the effect size depends on the invitation strategy used for offering self-sampling. We assessed if all socioeconomic groups of non-participants are being targeted by self-sampling and how the invitation strategy for offering self-sampling influences participation in different socioeconomic groups.

Results

The study was based on registry data applied to data from a randomized controlled trial (n=9,791) measuring the impact of HPV self-sampling on participation among Danish women aged 30-64 who were due to receive their second screening reminder. The women received either: 1) a self-sampling kit mailed directly to their homes (directly mailed group), 2) an invitation to order the kit (opt-in group), or 3) a standard second reminder to attend regular cytology screening by the general practitioner (control group). Women offered self-sampling were informed that they could also receive usual care if wanted. Participation data was analyzed according to intention-to-treat principle and linked to individual-level registry-data on socioeconomic factors.

Conclusion

Women in the directly mailed group participated more often than women in the control group, regardless of their socioeconomic status, but the largest effects occurred in Western immigrants (absolute participation difference (PD): 18.1%, 95% CI: 10.2-26.0%) and social welfare recipients (PD: 15.2%, 95% CI: 9.7-20.6%). Compared with the control group, opt-in self-sampling increased participation in almost all socioeconomic groups, but had an insignificantly effect on participation among women who were immigrants, retired, or less educated. Western immigrants had a significantly higher increase in participation than native Danish women when the kits were mailed directly, compared with the opt-in strategy (PD: 18.1%, 95% CI: 10.2-26.2% and PD: 5.5%, 95% CI: 2.9-8.1%, respectively)

References

All socioeconomic groups benefitted from the directly mailed strategy in terms of higher participation, but Western immigrants and social welfare recipients benefitted the most, implicating that the directly mailed strategy might be a promising tool to reduce social inequality in participation. Since immigrants and some lower socioeconomic groups had only insignificant effect of opt-in self-sampling, the directly mailed strategy might be favored over the opt-in strategy.

W3. Vulvar Diseases

00544

Vulvar dermatoses: Natural history of lichen sclerosus and lichen planus; risk for malignancy

24. Vulvar diseases and neoplasia

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Background / Objectives

WORKSHOP VULVAR DISEASES, SUNDAY, DEC. 2

Lichen Sclerosus (LS) and Lichen Planus (LP) are dermatosis which can affect also genital mucosa. Estimated prevalence for LS is 0.1–0.3% in a general hospital patient population and 1.7% in general gynecological practice. Respectively, LP prevalence among vulva clinic patients is estimated to be around 3.7%.

Malignany potential of both dermatoses have been suspected, but evidence is sparse. There is an association with vulvar LS and subsequent vulvar squamous cell carcinoma (SCC); the estimated risk of developing vulvar SCC in the areas affected by LS is up to 5%. In contrast, extragenital LS does not seem to be associated with malignant transformation.

There is an association between oral LP and oral squamous cell carcinoma (SCC). Also, some case reports of patients with LP and subsequent vulvar SCC exist.

Results

In this presentation pathways for vulvar cancer will be revaled. Vulvar HSIL lesions are more common, HPV based lesions. Differentiated VIN (d-VIN) is rare, but risk for malignancy is up to 30%. The current ISSVD terminology for vulvar precancerous lesions will be presented. In the older litterature there are some retrospective studies and case reports among LS and LP patients with vulvar cancer. There is also some evidence that compliance of the corticosteroid treatment decreases the risk of vulvar cancer.

Conclusion

Our own Finnish Cancer Registry data will be presented. We identified all women with the diagnosis of LS (n= 57,616), or LP (n=513,100) recorded in the Finnish

Hospital Discharge Registry from 1970 or 1969 to 2012. The cohort was followed through the Finnish Cancer Registry for subsequent cancer diagnoses until 2014. Standardized incidence ratios (SIRs) were calculated for different cancers by dividing the observed numbers of cancers by expected ones. During the follow-up period, we found 812 cancers among patients with LS (SIR: 1.13, 95% CI 1.05–1.21) and 1,520 with LP (SIR 1.15, 95% CI 1.09–1.20). LS was associated with an increased risk of vulvar (182 cases, SIR: 33.6, 95% CI 28.9–38.6) and vaginal cancer (4 cases, SIR: 3.69, 95% CI 1.01–9.44). LP was associated with an increased risks of cancer of lip, tongue, oral cavity, esophagus, larynx and vulva.

References

Patients with diagnosed LS is associated with an increased risk for vulvar and vaginal cancer. Treatment of the dermatose with corticosteroid may decrease this risk.The malignant potential of LP is not so well documented. However, in our own data, patients with LP have an increased risk of developing cancer of lip, tongue, oral cavity, esophagus, larynx and vulva. d-VIN is a precursor of vulvar cancer. These data are important when considering treatment and follow-up of patients with a diagnosis of these dermatoses.

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W5. WORKSHOP LUSÓFONO

00455

DETERMINANTS OF INFECTION BY HIGH-RISK HPV IN WOMEN: POPULATION-BRAZIL STUDY

02. Epidemiology and natural history

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Background / Objectives

Many types of human papillomavirus (HPV) were already described[1] and they are classified based on their carcinogenic potential[2,3]. High-risk HPV (HR-HPV) types are responsible for basically all cervical cancer (CC) cases. The type of HR-HPV infection is an important information to understand the dynamic of HPV infection and, thus, to develop prevention strategies. Although guidelines do not differ the risk among HR-HPV, some stains seems more aggressive. Therefore, the aim of this work was to estimate the prevalence of HR-HPV groups and its associated determinants

Results

POP-Brazil[4] is a multicentric study which enrolled participants by trained health care professionals in primary care units and answered an interview with sociodemographic (sex, age, race, social class, and smoke) and sexual (relationship status, condom use, age of first intercourse, and number of sexual partners in the last year) characteristics. A genital sample was collected and analyzed by Linear Array HPV Genotyping Test®. HPV groups were defined according to HPV CC risk[5,6,7]: HR1 corresponds to major risk types (16 or 18), responsible for more than 75% of CC cases; HR2, corresponding to the next five most carcinogenic types (HPV 31, 33, 45, 52 or 58); and HR3 (HPV 35, 39, 51, 56 or 59), less frequently found in CC. In all analyses, the data were weighted by population in each capital according to gender within age range of the study. Poisson with robust variance model was used to evaluate the association between sociodemographic and sexual

characteristics and HR-HPV groups. The analysis were adjusted by all characteristics, and we used SAS software, version 9.4 with significance level of 5%.

Conclusion

We included 5,268 non-vaccinated women. The prevalence of HR1 was 12.24%, HR2 was 20.06% and HR3 was 17.02% ($p < 0.001$). Age (0.69, 95%CI 0.55-0.86) and number of sexual partners (1.60, 95% CI 1.27-2.02) were associated with HR1. HR2 was also associated with relationship status (1.29 95%CI 1.05-1.58) in addition to age (0.72, 95%CI 0.60-0.85) and number of sexual partners (1.78, 95%CI 1.48-2.14). Besides associated with the same characteristics of HR2 [age (0.67, 95%CI 0.55-0.81), number of sexual partners (1.46, 95%CI 1.20-1.78), and relationship status (1.36 95%CI 1.09-1.68)], HR3 was also associated with being black (1.43 95%CI 1.10-1.94) and brown (1.46 95%CI 1.13-1.90).

References

The most oncogenic group (HR1) was found to be the less frequent one in the studied population. All groups share some risk factors as lower age (< 22 years) and number of sexual partner in the last year (>2), but the prevalence of HR3 was also associated with the race of participants. Preventive strategies should be focus in younger ages and some specific races as black and brown women.

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00359

HPV PREVALENCE, CHANGES ON CYTOLOGY AND HSIL PREVALENCE ON BIOPSIES IN HIV POSITIVE WOMEN

08. HPV testing

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Background / Objectives

Women infected with Human Immunodeficiency Virus (HIV) are about 5 times more prone to concomitant Human Papillomavirus (HPV) infection. Association of HPV with dysplasia and cervical cancer is well established; however, the most common type of cervical lesions and their frequency needs to be better characterized. Our objective was to assess the prevalence of HPV infection and cervical cytology/cervical biopsies findings in HIV-positive women.

Results

Retrospective study with data collected from medical record review of HIV-positive women followed up between 2008 and 2018 on the outpatient gynecological setting care of our hospital. Demographic and clinical variables were analyzed. Cases with no reference to HPV status were excluded.

Conclusion

273 women were included in our study; median age was 43 years (18-75 ys). Median age of first sexual intercourse was 17 years (12-34ys). Average number of sexual partners was 4 (1-10+). 51.4% of women were smokers (72 out of 140 with registered data). 15 women had concomitant C hepatitis infection, and 5 had simultaneous HIV, B and C hepatitis. There was only one case of rheumatoid arthritis in a C hepatitis co-infection and one case with chronic kidney disease. Regarding antiretroviral therapy (HAART), 85.4% of women (n=169) were under this therapy, while 14.6% (n=29) were not; information was missing in 133 cases.

Concerning HPV status, there were 29 cases of HPV-16 (10.6%), 19 cases of HPV-18 (7.0%) and 80 cases (29.3%) of high risk-HPV (HR-HPV). 26 women had simultaneous HPV-16/18; 20 had HPV-16/HR and 26 had HPV-18/HR.

Cervical cytology was negative on 143 cases (52.4%); in 60 cases (22%) inflammation was noted and 70 women (25.6%) showed abnormalities: 22 atypical squamous cells of undetermined significance (ASCUS); 1 ASC-H; 39 low-grade squamous intraepithelial lesion (LSIL) and 8 high-grade squamous intraepithelial lesion (HSIL).

Subsequent evaluation with biopsies in the subgroup with cytology abnormalities was as follows: ASCUS 13 cases (7 no lesion, 6 LSIL); one case of ASC-H had negative biopsy; LSIL 25 cases (11 no lesion, 8 LSIL, 6 HSIL); HSIL 8 cases, all with positive biopsy (1 LSIL, 7 HSIL). There was only one case of squamous cell carcinoma whose cervical cytology displayed inflammation and HPV-18 positivity. In total 47 cervical biopsies were performed: 19 negative, 15 LSIL and 13 HSIL.

References

Data from this population sample confirmed an elevated prevalence of abnormalities on cervical cytology (25.6%) compared with published results in non-HIV women. HSIL on biopsies was found in 13 patients (4.8%) with either LSIL or HSIL in cervical cytology. Although there was only one case of cervical carcinoma among 273 HIV-positive women, routine surveillance for cervical cancer in this group of women should be recommended.

00175

REEVALUATION OF HPV INFECTION IN WOMEN WITH NORMAL CERVICAL CYTOLOGY WITH NEGATIVE HPV TEST AFTER 5 YEARS

09. HPV screening

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Background / Objectives

HPV infection and persistence are the main risk factor for cervical cancer and screening for has decreased incidence and mortality. In women equal and above 30 years, co-testing (cervical cytology and HPV testing) is recommended every 5 years, if both initial tests are negative. A negative co-testing is related with low risk of developing HSIL within the next 5 years.

The aim of this study was to evaluate cervical HPV infection prevalence and abnormalities in the Pap smear in women with a previous negative co-test 5 years before.

Results

A retrospective study was conducted. Women with a normal cervical cytology with DNA negative HPV test in 2013 were included. In 2018, we repeated co-test to those women. Clinical and demographic data (age, age of menarche), reproductive features and behavior (age at first sexual intercourse, parity, oral contraceptive use, number of sexual partners, cigarette use) were recorded.

Conclusion

Seventy-nine (79) women were included. The median age was 51 years (range: 34-64). Seven (10%) were nulliparous, 22 (31%) primiparous and 42 (59%) multiparous. Menarche was at 12 years (median age; range: 10-17); first sexual intercourse median age was 19 (range: 14-34); sexual partners number was 1 (median; range: 1-15); 21

(30%) women were current or previous smokers and 33 (44%) declared history of hormonal contraception use. Reevaluation after 5 years revealed: 1 case of ASCUS with negative HPV test; 1 case of LSIL with negative HPV test; 1 case of LSIL with HR-HPV others than 16 and 18 positive; 1 case of normal cervical cytology with HPV 18 positive and HR-HPV others than 16 and 18 positive.

References

These very preliminary data have revealed that, after a 5 years lag time, 77 out of 79 women with co-test negative remained HPV negative and a very low rate for HPV infection (2/79 cases); abnormalities on cytology (ASCUS or LSIL) were minor at 5 years. Our findings are in support of the recommendations for cervical screening at 5 years interval in women with HPV DNA test. It is urgent to reinforce population information regarding the benefits on follow up.

00252

HIGH-RISK HUMAN PAPILLOMAVIRUS OTHERS THAN 16 AND 18 CERVICAL INFECTION AMONG WOMEN WITH NORMAL CERVICAL CYTOLOGY: RE-EVALUATION AT LEAST AFTER ONE YEAR

09. HPV screening

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Background / Objectives

High-risk human papillomavirus (HR-HPV) infection is currently a well-established cause of cervical cancer, but only few of the women who have persistent infection will develop cervical precursor and malignant lesions. HR-HPV infection, aside for serotypes 16 and 18, account for at least 20% of all cervical cancers worldwide. This study aimed to re-evaluate women who had a HR-HPV infection (serotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) with a normal cervical cytology.

Results

A retrospective study was conducted at a tertiary hospital which included women who had a HR-HPV infection (serotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and a normal cervical cytology. Women were re-evaluated (co-test) at least one year later. Demographic and clinical data were recorded and compared between women with persistent infection and without infection after re-evaluation.

Conclusion

One hundred and forty eight women were included from September 2012 to May 2018. The median age was 45 years (range: 30-65), 20.3% (n=30) were nulliparous and 48% (n=71) were multiparous. The median age of menarche was 13 years (range: 9-19) and the median age at first sexual intercourse was 18 (range: 12-41).

The median number of sexual partners was 3 (range: 1-40). Thirty six (24.3%) women were smokers and 47 (31.8%) were taking hormonal contraception. Re-evaluation (119 at 12 months, 20 at 24 months, 5 at 36 months and 4 at 48 months) revealed that 54.7% (n=81) women did not have HR-HPV cervical infection or an abnormal cervical cytology. Women with persistent infection had more abnormal cytological results (n=18 vs n=2, p<0.001). No other differences were found between the groups. Twenty women (13.5%) developed cervical precursor lesions (3.4% ASCUS; 8.8% LSIL; 1.4% HSIL) but two of these (1 LSIL and 1 ASCUS) had no persistent HPV-HR infection. In the group with persistent cervical infection with normal cervical cytology, two women also developed concomitant cervical infection with serotype 16 and one with serotype 18.

References

In our population, the re-evaluation of women with isolated HR-HPV (other than 16 and 18) cervical infection revealed that more than half of these women had a spontaneous regression of the infection and only 1.4% developed an HSIL.

00346

Prevalence and risk factors for HPV infection, cervical cytology anomalies and sensitivity of DNA HPV-HR test to detect high grade lesions in biopsies

09. HPV screening

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Background / Objectives

Persistent HPV infection is the major cause for cervical cancer and precursor lesions. High risk HPV (HPV-HR) carriers have significantly increased risk for high grade lesions and cervical neoplasia. The objective of this study is to evaluate the prevalence of HPV-HR (16,18 and 12 other genotypes), cervical cytology anomalies, risk factors associated with persistent HPV-HR infection and to compare the sensitivity of DNA HPV-HR test and of cervical cytology to detect histological high grade lesions (CIN2/CIN3+).

Results

Retrospective study (November 2012-June 2018).Women between 25 and 65 years were included in an opportunistic screening for cervical cancer. Liquid-based cytology technique and an adjuvant molecular test based on real-time PCR (DNA HPV-HR method) that detects HPV 16, 18 and 12 others high-risk HPV genotypes were performed. Data were collected from clinical files: age, parity, age at first sexual intercourse, number of sexual partners, hormonal contraception use (HC), smoking habits (SH) and results of cervical biopsies.

Conclusion

3019 cases were included and the median age was 47 years. The overall HPV-HR prevalence was 11.5% Out of the HPV-HR infected women, 241(69%) were HPV-HR others-positive, 54(16%) were HPV16-positive,13(3.6%) were HPV18-positive and 39(12%) had co-infection for several HPV-HR.The cervical cytology anomalies

prevalence was 5%: 93(51%) LSIL, 47(26%) HSIL, 9(5%) ASCH, 1(0.1%) AGC and 27(16.4%) ASCUS. The proportion of HPV-HR infected women with normal cervical cytology was 7.3%: HPV-HR others in 164(80%) cases, HPV16 in 20(9.7%) cases, HPV18 in 10(4.8%) and co-infection for several HPV-HR in 12(5.5%) cases. Considering women with infection with HPV-HR and women without infection with those virus, there were statistically significant differences concerning age, SH, HC, number of sexual partners and age at first sexual intercourse. The infection of HPV-HR decreased with age and was more common between 30-34 years old ($p<0.001$).It was statistically related with SH($p<0.001$), HC use ($p<0.001$), multiple sexual partners($p<0.001$) and younger age at first sexual intercourse($p<0.001$).In the studied population, the sensitivity to detect high-grade lesions (CIN2/CIN3+) in biopsies was 0.95(CI: 0.87-0.98) for DNA HPV-HR test and 0.70(CI: 0.57-0.79) for liquid-based cytology technique.

References

Our results are comparable with recently published data on HPV-HR prevalence distribution (more cases with HPV-HR others) and risk factors associated with infection such as SH, HC and sexual behavior. This study supports the highest sensitivity of DNA HPV-HR test compared with cervical cytology in the detection of high grade lesions in biopsies and may contribute for the scientific discussion about the use of DNA HPV-HR testing as a primary screening.

00364

WHAT IS THE ROLE OF HPV SCREENING IN WOMEN BETWEEN THE AGES OF 25 AND 29

09. HPV screening

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Background / Objectives

Human papillomavirus (HPV) infection persistence is the main cause for intraepithelial lesion and cervical cancer.HPV infection prevalence is significantly higher in women under 30 years, with a higher rate of spontaneous resolution.

Objectives: To evaluate HPV-High Risk (HPV-HR) prevalence, cervical cytology altered according Bethesda classification, and major risk factors in a convenience sample from Portuguese population.

Results

Retrospective study (November 2012 to June 2018) which included women between the ages of 25 and 29 who underwent opportunistic screening for cervical cancer. HPV detection in cervical cytology was performed for 14 types of HPV-HR, isolated HPV16 and 18 and other HPV-HR. The prevalence of altered cervical cytology was analyzed and the following parameters were collected: age, parity, age on onset of sexual life, sexual partners' number, combined hormonal contraceptives use (COC) and smoking. Women with human immunodeficiency virus (HIV) infection were excluded.

Conclusion

In the studied sample, 296 women with a mean age of 27 years (range 25-29) were included. The total prevalence of HPV-HR was 31.8% (n = 94); HPV-HR other than 16 and 18 types was the most frequent 26.7% (n = 79). The prevalence of altered cervical cytology corresponded to 16.6% (n = 49).

Out the women without cervical cytology abnormalities (n = 247), 76.5% (n = 189) presented negative genotyping. The remaining data are the following: HPV16 was present in 3.2% (n = 8), HPV18 in 1.2% (n= 3), and other types HPV-HR in 21.1% the cases (n = 52); in 2% (n = 5) of the sample there was a presence of more than one subtype of HPV-HR.

The prevalence of stratified cytological changes according Bethesda classification showed that the presence of LSIL was the most common alteration (61.2%, n = 30), followed by ASC-US in 18.4% (n = 9), HSIL in 14.3% (n = 7) and ASC-H in 6.1% (n= 3). Twenty-eight cases were submitted to biopsy: one carcinoma in situ, five CIN 3, fifteen CIN 2, five LSIL and two biopsies with no abnormal findings. There was no case of AGC. In the subgroup of women with cytology abnormalities there was absence of HPV-HR infection in 26.5% (n=13). In the group of women with HPV-HR positivity, there was a statistically significant relationship with the use of tobacco ($p<0.005$) and higher number of sexual partners ($p\leq0.005$), but no significant relationship with the age on onset of sexual life.

References

In this population, HPV-HR presence was more prevalent than Pap smear abnormalities; HPV-HR others than 16 and 18 are the most prevalent; we find 58 cases with HPV-HR positivity despite a negative cytology; smoking and sexual partners number were significantly related with HPV-HR positivity; the HPV DNA HR test shows high sensitivity for HSIL detection on biopsy.

00413

HPV screening: are old women demanding new strategies?

09. HPV screening

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Background / Objectives

Human Papillomavirus (HPV) screening is at the forefront of cervical cancer detection. Data from different studies and health population records had shown that cervical cancer associated mortality is increasing in elderly women. Consensus for Portuguese cervical cancer screening recommends its ending at age 65 and according to the 2011 CENSOS, 21.5% of women are over this age. Has our primary screening been ignoring an important age group? For the first time in Portugal, we aim to evaluate the prevalence of high risk HPV (HR-HPV) infection in a group of Portuguese elderly women.

Results

Women aged 66-75 years attending a menopausal setting between 2014 and 2018, with no previous HPV screening, were offered a cytology and DNA HR-HPV screening. Demographic data and cervical cancer risk factors (age of first sexual intercourse, number of sexual partners, oral contraceptive use, smoking history and parity) were obtained from clinical files.
A cervical specimen was collected and sent to cytological evaluation (*Bethesda* system) and for HR-HPV screening, using the COBAS ® test.

Conclusion

A total of 259 women were included, the median age was 71 years (66-75). Menarche median age was 13 years (8-18) and women were mainly multiparous (69.2%). Median age of first sexual encounter was 22 years (15-34) and the mean number of sexual partners was 1.2 (1-4). Most women did not have a history of smoking (89.2%) and have not used oral contraceptives (57.1%).
A single case of isolated HPV-18 infection and another of isolated HPV-16 were

detected. One case was co-infected with HPV-16 and other HR-HPV than 16 and 18 and 9 women were infected only with other HR-HPV (HPV16-/HPV18-). Thus 4.6% of women (n=12) were infected with HR-HPV.
The vast majority of cytological samples were classified as *NILM* (98.8%, n=256), of which 34.4% (n=88) had inflammatory related changes. Pap smear revealed two cases of *ASC-US* and one case of *ASC-H*, in a patient with a negative HR-HPV screening.

References

Our results show a prevalence of HR-HPV similar to what previous studies have reported in this age group.
The prevalence of HR-HPV was low comparing with younger age groups. Accordingly, this was a population with a low risk for HPV infection as demonstrated by its pattern of risk factors. Yet, shifts in cultural patterns will probably result in future elderly populations with different sexual behavior, higher rates of smoking and higher rates of oral contraceptive use.
Optimization of population based screenings is a real challenge. Therefore, further studies are needed because guidelines must be dynamic and adapted to shifting realities.

00516

HPV TESTING FOR CERVICAL CANCER SCREENING: EXPERIENCE IN CENTRO MEDICINA LABORATORIAL GERMANO DE SOUSA/HOSPITAL CUF DESCOBERTAS

09. HPV screening

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Background / Objectives

The spread of HIV epidemics globally has increasingly drawn attention to the interaction between HIV and the “classic” sexually transmitted infections (STIs). A consensus has grown that other STIs increase the spread of HIV, following on from the early epidemiologic studies that explored the epidemiologic synergy between STIs and HIV. However, the interaction of the many STIs with HIV is potentially complex, with the possibility of reciprocal influences on susceptibility, infectiousness, and the natural history of infections. There is growing evidence of a significant burden of human papillomavirus (HPV) infection and associated disease in men. HIV infection increases HPV prevalence, incidence, and persistence and is strongly associated with the development of anogenital warts as well as anal, penile, head and neck cancers in men. Despite increasing access to antiretroviral therapy, there appears to be little benefit in preventing the development of these cancers in HIV-positive men, making prevention of infection by vaccination and information, a priority.

The authors present 5 years revised casuistic as a reference laboratory center in sexually transmitted infectious diseases diagnosis.

Results

Male samples were tested by HPV-molecular and conventional-cytology methods. HPV molecular methods used where: Hybrid Capture 2 (hc2, Digene); Clart human papillomavirus 2 (Genomica) and PapilloCheck. The cytological results were registered with the comprehensive classification system, multi-axial nomenclature SNOMED. The diagnosis of “classic” sexually transmitted infections (STIs) as Herpes Simplex virus 1 and 2, Syphilis, Gonorrhea, Chlamydia trachomatis, Ureaplasma and Mycoplasma infections statistics were used for data analysis; the Fisher exact test

was employed to assess the association between categorical variables. *P-values* (2-sided test) less than 0.05 were considered significant.

References

This study will contribute to a better understanding of the wide spectrum of male HPV infection.
The results obtained for the incidence of most frequent HPV genotypes in men and MSM are in agreement with several studies [Dunne EF, 2006]. The most common anogenital HPV types detected in men varied by study but were similar to the types commonly detected in women.

Type 16 was consistently found among the most common; however, other types were also reported (types 6, 11, 18, 31, 33, 42, 52, 53, 54, 59, and 84) [Dunne EF, 2006], but a shift possibility can occur with universalization of the vaccine.
On genotyping tests multiple infections decreased by the severity of the cytological interpretation, revealing that persistent and relapsing HPV infections are at higher risk for anal dysplasia development and malignant transformation. HPV infection appears to occur early in MSM.

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00321

RISK FACTORS FOR HPV INFECTION AND DUAL STAIN FOR TRIAGE TO COLPOSCOPY. A COMPARATIVE PRELIMINARY STUDY

12. Molecular markers

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Background / Objectives

Most Human papillomavirus (HPV) infections are transient with less than 10% of infections actually progressing to high-grade lesions or cancer. Therefore, many women undergo additional unnecessary procedures as colposcopy and cervical biopsies. The dual stain test (DST) might optimize cervical cancer screening by using biomarkers as a tool to identify women that are at an increased risk and reduce the number of women submitted to colposcopy.

The aim of this preliminary study was to compare women with positive or negative DST in order to evaluate if known risk factors for HPV infections interfere with the DST result.

Results

Retrospective case-control study from February to June 2018.

It was performed DST to all women with atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells (ASC-H), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) cytology results and/or HPV-positive women (HPV-16, HPV-18, other high risk HPV). The studied population was divided in two groups, women with negative or positive DST. We compared demographic data, cervical cancer risk factors (age of first sexual intercourse, number of sexual partners, parity, oral contraceptive use and smoking habits) and comorbidities (HIV infection, autoimmune diseases and immunosuppressive treatments) between the groups. Statistical analysis was performed with IBM SPSS Statistics 20 (Mann-Whitney U test and Fisher exact test).

Conclusion

A total of 75 women had criteria to undergo DST (37/75 had a negative test). The group with a positive test was younger (median age 36 vs 48 years, p=0.015), had a higher number of sexual partners (median 4 vs 2, p=0.005), had less postmenopausal women (10.5% vs 47.2%, p=0.001) and more women HIV positive (81.8% vs 18.2%, p=0.047).

We found no differences for parity, oral contraceptive use, smoking habits, age of first sexual intercourse, autoimmune diseases or immunosuppressive treatments. Equally, there were no differences related to the type of high risk-HPV or cytology result previous to the DST.

References

Positivity for DST in these population sample and preliminary evaluation was found in nearly half of the women, and it was significantly related with younger age, sexual multiplicity and HIV concomitant infection.

00282

PREAVALENCE OF CYTOLOGY RESULTS AT A PRIVATE LABORATORY IN SAO PAULO - BRAZIL

13. Screening methods

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Background / Objectives

The method of choice for cervical cancer screening in Brazil is cervico-vaginal cytology (1). There is no complete and accessible official data on the prevalence of cytologic abnormalities in our country. The objective of the present study was to determine the prevalence of abnormal cytologic smears in a population of a large Brazilian city

Results

A retrospective study assessing results of cervical-vaginal cytology smears performed at a private laboratory in São Paulo city – SalomãoZoppi Diagnósticos, between January 2010 and December 2015 was conducted. The patients attended by this laboratory have health insurance.

Conclusion

A total of 1,030,482 cytology tests were performed between January 2010 and December 2015. We observed negative results in 91.1% (935,300) and altered in 8.9% (91,371). Table 1 shows the prevalence of the altered cytological results, according to the total cytology and according to the altered cytology.

Table 1 – Prevalence of cytologic abnormalities from 2010 to 2015

Cytological abnomarlity	n	Among all abnormal results (%)	Among all sample (%)
ASC-US	66878	73,19	6,514
LSIL	18729	20,50	1,824
ASC-H	2459	2,69	0,240
HSIL	1859	2,03	0,181
AGC	1355	1,48	0,132
HSIL-suggestive of invasion	50	0,05	0,005
Adenocarcinoma	28	0,03	0,003
SCC	13	0,01	0,001

Analyzing the different age groups, there is a clear increase in the prevalence of ASC-US with advancing age. This must be justified by the greater atrophy in older women and possible collection difficulties. The prevalence of LSIL falls after 30 years; this high prevalence of low-grade lesions in women younger than 30 years can be explained by the high prevalence of HPV infection. The AGC presented two peaks of elevation, in the range of 40-49 years and another peak in patients over 70 years. These peaks coincide with the age ranges that this abnormality is related to. Although a cytologic abnormality is not very prevalent, it is somewhat worrying. On the other hand, HSIL shows two peaks of elevation, respectively in the 30-39 year and 70 year old ranges, which is justified by the natural history of HPV with the peak incidence of low grade lesions before 30 years and, with a period estimated from 10 to 15 years for lesion development, the peak incidence of high grade lesions occurs in the following decade.

References

The data found show that there are patterns in the prevalence of cytological abnormalities that should be considered for the quality of population screening. Women under the age of 30 present a higher prevalence of low-grade lesions and this fact should be considered when interpreting the results in women in this age group. On the other hand, in older women, the rate of ASC-US and AGC increased, suggesting greater difficulty in reading these sheets and the need for HPV testing in this age group should be considered.

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00196

HIPERCERATOSE EPIDERMOLÍTICA COMO DIAGNÓSTICO DIFERENCIAL DE MANIFESTAÇÕES CUTÂNEAS CAUSADAS PELO HUMANO PAPILOMA VÍRUS: RELATO DE CASO

29. Genital warts

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Background / Objectives

O Papiloma Vírus Humano (HPV) é um vírus de DNA que apresenta tropismo por células epiteliais causando diferentes formas de infecção de pele e mucosas[1] , sendo as verrugas a manifestação clínica mais comum e característica do HPV[2] , afetando diversos locais, mas, principalmente, a região genital. O presente trabalho possui como objetivo relatar caso de paciente com Hiperceratose Epidermolítica atendida no Hospital Universitário Professor Alberto Antunes (HUPAA).

Results

Estudo descritivo e observacional de relato de caso de paciente, 34 anos, procedente de Maceió-Alagoas, encaminhada ao serviço de ginecologia do HUPAA por suspeita de condiloma acuminado provocado por HPV. Os dados foram colhidos no prontuário da mesma.

Conclusion

Apresentamos um caso de uma paciente do sexo feminino, 34 anos, sexualmente ativa, com surgimento de duas lesões cutâneas em região vulvar com início cerca de um ano antes do atendimento. O exame ginecológico encontrava-se normal. Durante a consulta, observou-se que as lesões apresentavam característica condilomatosa, hipercrômica e hiperceratósica em região de monte púbico, com espessamento de pele local. Devido à localização pouco comum da lesão e presença de hiperceratose associada, foi realizado biópsia das lesões, que, veio com resultado histopatológico de Hiperceratose Epidermolítica.

References

Essa manifestação histológica se caracteriza por ser uma doença genética da queratinização com transmissão autossômica dominante, porém, pode evoluir em 50% dos casos com mutação espontânea e tem uma prevalência de 1:100.000 a 1:300.000 pessoas distribuídas igualmente em ambos os sexos[3,4,5]. Não existe cura para a doença relatada sendo que o tratamento visa a redução dos sintomas, como descamações e fissuras, minimizando as infecções de repetição e devendo ser individualizada para cada paciente[6,7].

References

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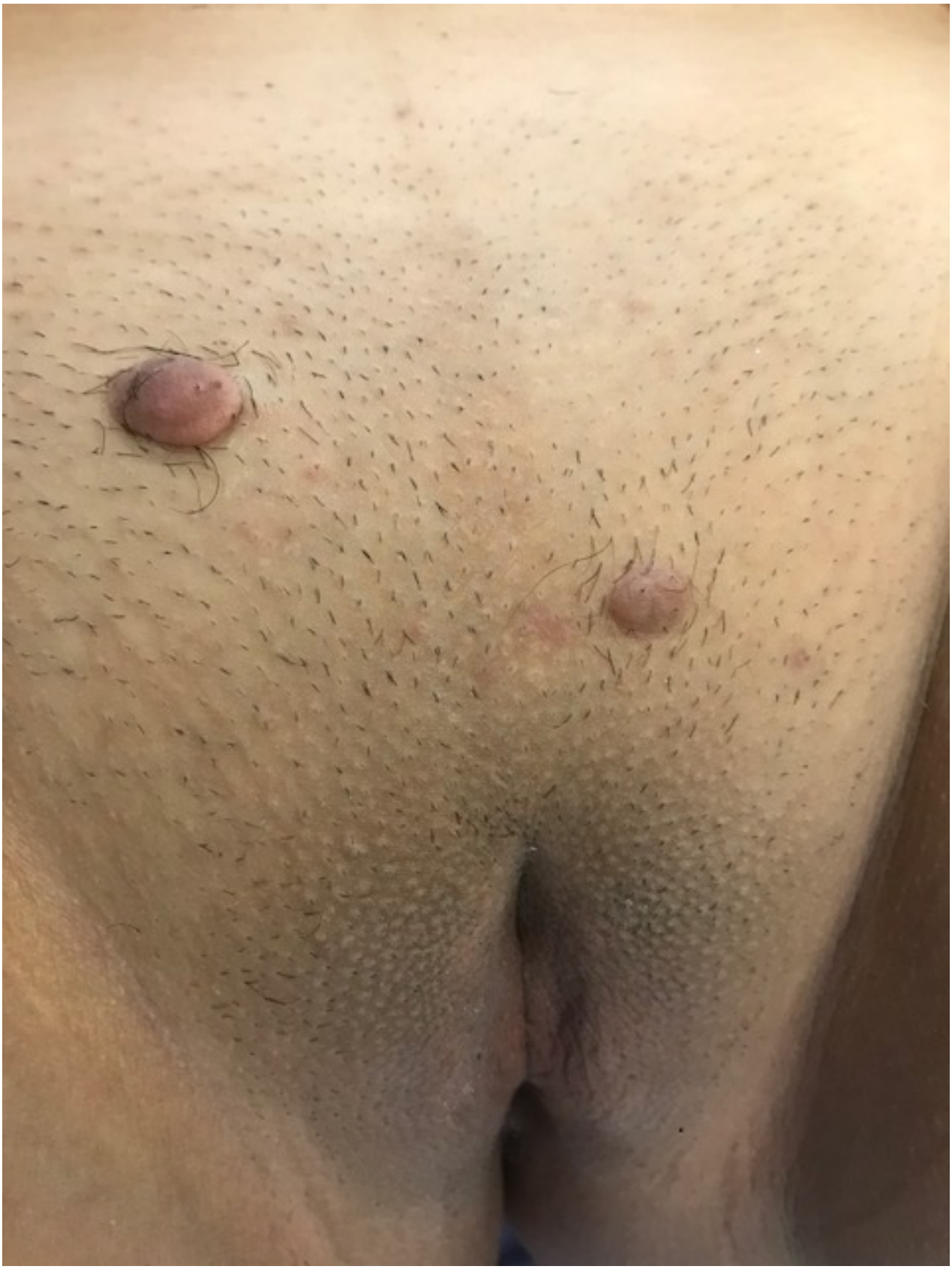

00507

PATTERN OF SEXUALLY TRANSMITTED INFECTIONS IN HUMAN PAPILLOMAVIRUS POSITIVE WOMEN OF CHILDBEARING AGE

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

Sexually transmitted infections (STIs) are fairly common in women of childbearing age. Co-existing STIs have been considered as important cofactors for human papillomavirus (HPV) infection and related carcinogenesis. Our aim was to determine the association between the presence of microorganisms of gynaecological importance, sexual behaviour, clinical and demographical variables and the HPV infection.

Results

Cervicovaginal self-collected samples from 680 Portuguese women of childbearing age (15-44 years) were tested for HPV, herpes simplex virus 2 (HSV-2), *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) by polymerase chain reaction. Sociodemographic, behavioural and clinical data were assessed at baseline through an anonymous self-administered questionnaire.

Conclusion

Overall, 28.2% women had one or more pathogens identified;the most frequent was HPV (17.5%), followed by CT (10.9%), HSV-2 (2.5%), NG (1.3%), MG (1.2%) and TV (1.0%). The highest prevalence rate of coinfections was observed for the age-range 20–24 years and for women who reported smoking habits, ≥ 2 lifetime sexual partners, prior pregnancies and condom or oral contraceptive use. Among HPV-positive women (n=119), 69.7% were positive for HPV only; 26.9% were coinfected with CT or NG or TV or MG or HSV-2, and 3.4% with mixed pathogens. Oncogenic HPVs were the most commonly detected genotypes in coinfected women. Considering HPV-negative

women (n=561), 12.3% had a single pathogen, while 0.5% had mixed pathogens. There was a 2- and 6- fold increased probability of having one and multiple pathogensin HPV-positive women (P=0.001 and P=0.022), respectively.

References

The knowledge of HPV prevalence may identify females at risk for cervical cancer. Additionally, molecular detection of other STIs associated with HPV acquisition and persistence may contribute to the prevention of precursor lesions and cervical cancer. Epidemiological data on STIs and related risk factors are important for the development of successful prevention, diagnosis and management strategies, namely to the design of ideal HPV vaccines directed to genotypes of greater regional prevalence.

00450

HPV INFECTION AMONG SEXUALLY ACTIVE YOUNG ADULTS IN BRAZIL

36. Public health

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Background / Objectives

The prevalence of HPV was already evaluated in some specific groups and regions, however there is no data on HPV prevalence in young general population or including all different regions of Brazil. So, this study aimed to report the prevalence of genital HPV infection in a nationwide sample of adolescents and young adults, who uses the public health system.

Results

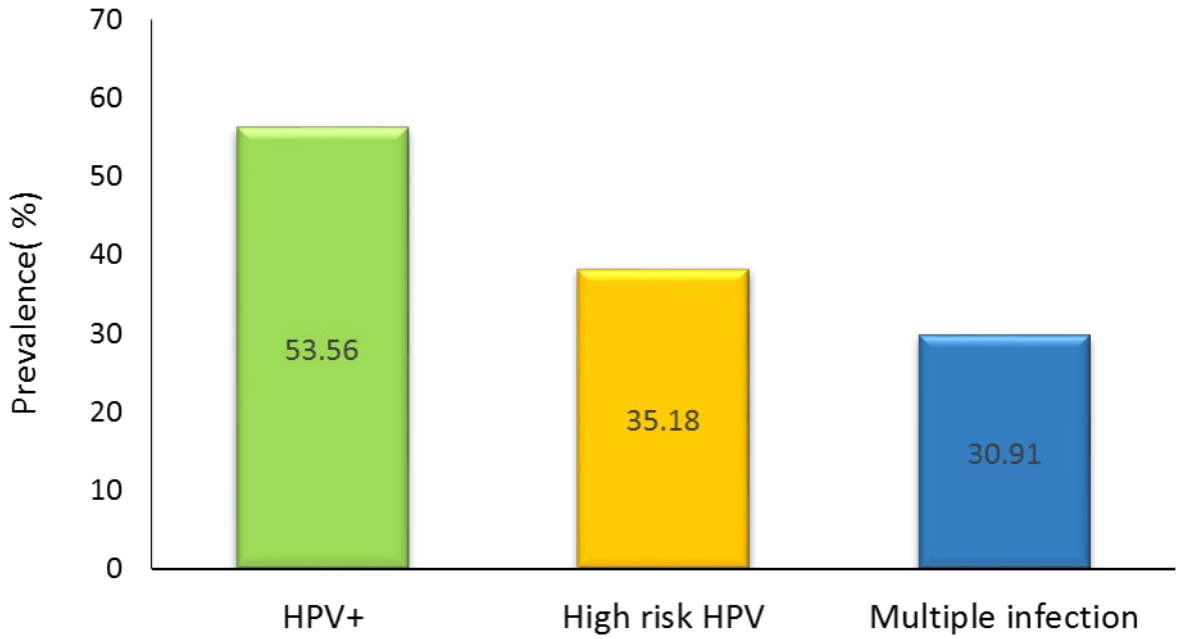
POP-Brazil Study is a cross-sectional nationwide survey who included sexually active women and men aged 16 to 25 years old. Participants were recruited in 119 primary care units by trained health professionals between September of 2016 and November of 2017. All participants answered a face-to-face interview and provided biological samples for genital HPV analysis. We used an automated DNA extraction method (MagNA Pure LC 2.0, Roche Molecular Systems) and HPV genotyping was performed on all specimens using the Roche PCR-based Linear Array Genotyping Test (LA). In all analyses, the data were weighted by population in each capital according to sex within age range of the study. The association between demographic and behavioral characteristics and HPV prevalence was evaluated trough Chi-squared test or Student’s t test with significance level of 5%.

Conclusion

From 7,693 participants included in the study, the majority declared themselves as brown (56.79%), were not engaged in a formal relationship (65.76%) and pertained to the social class C (56.11%). Although most participants referred to use condom, less than 40% did use it in the last intercourse. The mean age of participants at first sexual intercourse was 15 years and the majority had only one partner in the past year. Of 6,387 with valid samples (63.60% women), 53.56% (95% CI 51.37-55.75) were positive for any HPV type, with no differences between females (54.55%; 95% CI 52.52-56.59) and males (51.82%; 95% CI 46.98-56.66; p = 0.31). When stratified by age groups, there was a significant difference with higher prevalence of infection in the 16-21 years old group (56.65%, 95% CI 53.61-59.70) comparing to 22-25 years old (50.03%, 95% CI 46.86; 53.19). The presence of HPV types included in the quadrivalent vaccine (6, 11, 16 and 18) was detected in 14.95% of the specimens examined, being present in 27.92% (95% CI 25.45-30.40) of the infected people, without significant differences between genders (p = 0.26).

References

We found a high prevalence of HPV in a nationwide unvaccinated sample from Brazil. The pattern of HPV infection varied widely between genders. Knowledge of the distribution of HPV types in the population will enable evaluation of HPV effectiveness vaccination in the future.



W6. WORKSHOP FRANCOPHONE

00560

HPV VACCINATION IN BOYS AND MALES

05. HPV prophylactic vaccines

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Background / Objectives

At first, HPV immunization was aimed at the prevention of the cancer of the uterine cervix. It was therefore consistent to limit the vaccination to females, especially as a herd-immunity effect was expected in case of high coverage insuring a break in transmission of the virus.

Results

The rational of HPV immunization has changed following more extensive knowledge of HP-induced pathologies and reviewing the implementation of the HPV vaccination.

Conclusion

A reluctance to a “sexual” immunization has been observed in teens parents in many countries. Herd immunity, which requires high coverage rates has not been obtained in most countries. More importantly, HPV-related burden concerns both sexes. HPV is the most frequent STI and rates of genital HPV among males are similar to that in females. Yet a lower immune response to natural infection in males may account for higher prevalence of HPV infections. In addition to cervical cancer, HPV-induced cancers concern vulva, vagina, penis, anus and some head and neck tumors. Overall, HPV could be responsible for 5,2% of all cancers. At the same time some studies have shown HPV vaccination effectiveness is similar in both sexes and gender-neutral vaccination can be cost-effective.

References

Since HPV-inducted pathologies concern both sexes and account for a significant number of cancers it seems rational to move on to gender-neutral vaccination as it has been implemented already in several countries

HEAD AND NECK FORUM

HN1. Epidemiology of oral HPV infection

00554

THE NATURAL HISTORY OF ORAL HPV INFECTION

26. Oral HPV infection

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The University of Texas MD Anderson Cancer Center - Houston (United States of America)

Background / Objectives

The incidence of oropharyngeal cancer (primarily the tonsils and the base of the tongue) attributed to human papillomavirus (HPV), in particular type 16, is increasing at an alarming rate; therefore, understanding the natural history of oral HPV infection is paramount to ongoing prevention efforts. The natural history of HPV infection varies significantly between anatomical sites. While anogenital HPV infection is common, oral HPV infection occurs much less commonly. Significant risk factors for oral HPV infection include male sex, increasing age, cigarette smoking, and sexual behaviors. Men are more than twice as likely as women to have a prevalent oral HPV infection. This difference has mainly been attributed to differences in oral sexual behaviors, with men, on average, having higher numbers of oral sex partners than women. Furthermore, female to male genital to oral transmission rates appear to be higher than vice versa. Due to the relative rarity of oral HPV infection, longitudinal studies with adequate power to delineate the natural history have been difficult. Persistent infections are rare and most tend to clear within two years. Increasing age, male sex, and current smoking status have all been associated with oral HPV persistence. Although a persistent infection is assumed to be necessary for malignant transformation, a premalignant lesion has yet to be identified in the oropharynx. Based on population prevalence rates of oncogenic oral HPV infection and incidence rates of HPV-related oropharyngeal cancer in the United States, a latency period of 10-30 years from infection to progression to cancer has been estimated. Fortunately, there is emerging evidence that HPV vaccination prevents oral HPV infection. Lower point prevalence rates four years post-vaccination among women who received the HPV vaccine compared with women who received placebo as well as reduced prevalence of vaccine-type oral HPV among vaccinated young adults in the United States have been reported. It is therefore anticipated, although remains unproven, that prevention of oral HPV infection through vaccination will lead to significant reductions in HPV-related oropharyngeal cancer.

Results

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References

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00598

Tobacco and other risk factors for oral HPV

26. Oral HPV infection

G. Dsouza

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Background / Objectives

This talk will review what is known about risk factors for oral HPV infection. The association between tobacco and oral HPC infection and persitence will be discussed. Stratification of oral HPV risk by these risk factors presented.

Results

In session: HN1: Epidemiology of oral HPV infection

References

00493

INCIDENCE TRENDS IN HUMAN PAPILLOMAVIRUS (HPV)-ASSOCIATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA SUBSITES IN THE UNITED STATES AND CANADA, 1995-2015

27. HPV and oropharynx / Head and neck cancer

N. Osazuwa-Peters [1], M. Simpson [1], A. Bukatko [1], E. Adjei Boakye [2], K. Mohammed [1], N. Panth [3], R. Sethi [4], M. Varvares [4]

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Background / Objectives

The incidence of human papillomavirus (HPV)-associated head and neck (oropharyngeal) cancer has increased dramatically in the United States in the last three decades, and it is currently the leading HPV-associated cancer. No previous studies have described the incidence trends among the oropharyngeal cancer subsites that are most associated with HPV. We aimed to describe incidence trends in HPV-associated oropharyngeal squamous cell carcinoma in the United States and Canada by oropharyngeal subsites.

Results

Age-adjusted incidence rates of HPV-associated oropharyngeal cancer were calculated from the North American Association for Central Cancer Registries (NAACCR) database (1995-2015) covering the United States and Canada. Rates were stratified by anatomic subsites (palatine tonsil, base of tongue, lingual tonsil, soft palate/uvula, oropharynx proper, and pharynx), and presented per 100,000 person-years (PY). Overall rates for the entire study period, rate ratios (RR), and percent changes (PC) comparing the 1995 rate and 2015 rate were calculated for each subsite. Joinpoint regression estimated increases/decreases in age-adjusted incidence over time for each subsite through average annual percent changes (AAPC).

Conclusion

There were 271,223 cases in our cohort; predominantly males (79%), and non-Hispanic whites (78%). Most common oropharyngeal subsites were palatine tonsil (41%) and base of tongue (35%). The overall incidence was 4.10 per 100,000 PY with an AAPC of 2.28 ($p < 0.01$). Overall, age-adjusted incidence rate increased by 53% from 1995-2015 (3.19 per 100,000 PY in 1995, and 4.90 per 100,000 PY in 2015). Patients with palatine tonsil (AAPC=3.30), base of tongue (AAPC=3.10), and oropharynx proper (AAPC=1.70) experienced significant rate increases from 1995-2015 ($p<0.01$), while rates decreased for soft palate/uvula (AAPC=-3.27, $p < 0.01$). Rates remained stable for lingual tonsil and pharynx. Palatine tonsil also had the highest incidence rate from 1995-2015 (1.67 per 100,000 PY), followed by base of tongue (1.43 per 100,000 PY), and oropharynx proper (0.42 per 100,000 PY). Compared with palatine tonsil, all other oropharyngeal subsites had significantly lower rates (RR range=0.07-0.86, $p < 0.05$).

References

In the United States and Canada, the incidence of HPV-associated oropharyngeal cancer has increased by more than 50% in the last two decades, especially in the palatine tonsil and base of tongue. There is need for targeted primary prevention efforts to decrease the ever-increasing incidence of HPV-associated oropharyngeal cancer.

References

HEAD AND NECK FORUM

HN2. Recurrent metastatic HPV related cancer

00576

FUNCTIONAL ACTIVE TUMOR-SPECIFIC T CELLS IN OROPHARYNGEAL CARCINOMA ARE REQUIRED FOR OPTIMAL CLINICAL RESPONSE TO STANDARD THERAPY

04. Immunology

M. Welters [1], R. Goedemans [1], P. Charoentong [2], E. Jordanova [1], I. Ehsan [1], S. Santegoets [1], V. Van Ham [1], V. Van Unen [1], F. Koning [1], Z. Trajanoski [2], S. Van Egmond [1], S. Van Der Burg [1]

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Background / Objectives

The number of patients with HPV+ oropharyngeal squamous cell cancer (OPSCC) is still increasing and their clinical outcome upon standard therapy is favored by the presence of HPV as compared to HPV-negative (HPV16-) OPSCC patients. Previously, we have shown that the expression of virally-derived oncoproteins E6 and E7 on tumor cells elicit an immune response and recently we investigated this in more detail.

Results

Tumor tissue of OPSCC patients obtained prior to treatment was prepared for single cell analysis and culturing infiltrated lymphocytes (TILs). Phenotypical (36 parameter mass cytometry (CyTOF), flow cytometry) and functional analysis (proliferation, cytokine production, flow cytometry) upon stimulation with HPV16 E6 and E7 or control antigens were performed. In addition, paired peripheral blood mononuclear cells were subjected to CyTOF analysis for comparison. FFPE was used for HPV DNA typing, p16INK4a staining and quantification of T-cell infiltration analysis by fluorescent triple staining. Data was correlated to overall survival (OS).

Conclusion

64% of HPV16+ OPSCC patients displayed intratumoral HPV16-specific CD4+ and CD8+ T-cell responses and this correlated to a better OS. The HPV-reactive T cells produced IFNg, TNFa and/or IL-17 revealing a mixed Th1/Th17 profile. Moreover, CyTOF analysis showed that these TILs were effector memory T cells with a highly activated phenotype (CD38+, HLA-DR+ and/or PD-1+). However, also regulatory T

cells (Tregs) were found to be present in the tumor as stained by FoxP3. Interestingly, the majority of these tumor infiltrated T cells, including the Tregs, expressed the transcription factor Tbet and the numbers of Tbet+ T cells was highest in the patients showing an HPV-specific immune response as well as correlated with improved OS.

References

Patients with HPV-specific T-cell responses observed in their pre-treated HPV16+ OPSCC have an improved clinical outcome upon standard therapy. Tbet+ Tregs co-infiltrate in the inflamed tumor possibly to suppress pathological immune responses (i.e. the HPV-specific T-cell response) as their normal mode of action, however, they insufficiently suppress the infiltrated effector T cells given the fact that the patients with HPV-reactive T cells have survival benefit.

References

Intratumoral HPV16-specific T-cells constitute a type 1 oriented tumor microenvironment to improve survival in HPV16-driven oropharyngeal cancer. Welters MJP, Ma W, Santegoets SJ, Goedemans R, Ehsan I, Jordanova ES, van Ham VJ, van Unen V, Koning F, van Egmond SL, Charoentong P, Trajanoski Z, van der Velden LA, van der Burg SH. Clin Cancer Res. 2018, 24(3):634-647.

The anatomical location shapes the immune infiltrate in tumors of same etiology and impacts survival. Santegoets SJAM, van Ham JJ, Ehsan I, Charoentong P, Duurland CL, van Unen V, Höllt T, van der Velden LA, van Egmond SL, Kortekaas KE, de Vos van Steenwijk PJ, van Poelgeest MIE, Welters MJP, an der Burg SH. Clin Cancer Res. 2018 (in press)

00276

Immunocheckpoint inhibitors (ICIs) for recurrent/metastatic (R/M) oropharyngeal cancer (OPC) patients. Do HPV-related patients benefit most from these treatments?

07. Immunotherapy - Immuno-oncology - New treatments

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Background / Objectives

HPV status is an independent predictor of improved overall survival in OPC patients, even in the R/M setting. However, the combination of platinum, flurouracil and cetuximab (EXTREME regimen) has remained the uniform standard treatment in the first line HPV-related and unrelated R/M disease for the past 10 years. In a retrospective analysis of this trial, HPV related tumors were associated with a more favourable outcome but de survival benefits of chemotherapy plus cetuximab compared with chemotherapy alone were independent of HPV status. Recently, the KEYNOTE-048 trial has shown the superiority of pembrolizumab in monotherapy to the EXTREME schedule in patients with PDL-1 expression greater than 20% by combined positive score (CPS). This could change the actual standard of care treatment in first-line R/M head and neck squamous cell carcinoma (HNSCC). PD-L1+ tumors in general tend to demonstrate improved response rates to antiPD-1/PD-L1 therapy (ICIs) when compared to PD-L1- tumors. This correlation has been consistent with different antiPD-1/PD-L1 agents across multiple tumor-types, including head and neck cancers. Furthermore, HPV-related OPC express higher rates of PD-L1 compared to HPV-negative OPC samples. The question is, in this new era of ICIs for R/M disease: do HPV-related tumors benefit most from ICIs?

Results

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Conclusion

Considering the potentially worsening of some of these patients treated with ICIs (hyperprogression and fast progression), the severe immune-related toxicities and the high cost of these drugs, the search for predictive biomarkers of response is crucial. Hypothetically, virus-related tumors should be more responsive to ICIs due to intrinsic characteristics including increased baseline tumor immunogenicity and increased PD-L1 expression. This hypothesis was initially supported by the results from the R/M HNSCC cohort of the phase I KEYNOTE-012 trial in which HPV-related tumors had increased overall response rate to pembrolizumab compared to those that were HPV negative (30% vs 14%). However, these results were not reproduced in the phase III KEYNOTE-040 trial and have been unclear across other studies. Indeed, in the CHECKMATE-141 study, nivolumab only found differences in overall survival in the subgroup analysis of HPV-related/PDL1+ patients, but not in the PDL-1 negative ones.

References

We are still gathering knowledge from the use of ICIs in other tumor types. The results from the first phase III studies investigating the role of ICIs in R/M HNSCC are just showing up and there is no solid data regarding the patients with HPV-related tumors. Other biomarkers, such as smoking status, tumor mutational burden, interferon-gamma signature or the microbiome may give us more light in predicting response to ICIs in HPV-related and unrelated OPC types.

References

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00555

Human Papillomavirus-associated Oropharyngeal Cancer in an Aging Population

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papillomavirus - associated oropharyngeal cancer (HPV-OPC) is no longer strictly a disease of the young.

Results

The incidence of HPV-OPC is rising among adults of all ages including those over age 65, a trend which is projected to continue. Recent analyses have demonstrated that the prognostic advantage conferred by HPV-positive compared with HPV-negative tumor status persists among older adults, although survival among older adults compared with middle-aged and younger may be attenuated. Reasons for this attenuation are unclear, but may reflect the unique needs of older adults. Older patients are thought to have a narrower therapeutic window resulting in greater toxicity from treatment. Furthermore, these patients tend to have a greater number of comorbidities, and require more supportive care. As clinical trials are generally exclusive of this demographic, whether treatment recommendations should be different by age remains unclear. Research on the needs of older adults with HPV-OPC in treatment and survivorship and its implications will be discussed.

References

Research on the needs of older adults with HPV-OPC in treatment and survivorship and its implications will be discussed.

HEAD AND NECK FORUM

HN3. Recurrent respiratory papillomatosis

00566

QUALITY OF LIFE AND PSYCHOSOCIAL EFFECTS IN PATIENTS WITH RRP

26. Oral HPV infection

M. San Giorgi [1], L. Aaltonen [2], R. Tjon Pian Gi [1], B. Van Der Laan [1], J. Hoekstra-Weebers [3], F. Dikkers [4]

[1]Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen - Groningen (Netherlands), [2]Department of Otorhinolaryngology-Head and Neck Surgery, University of Helsinki, Helsinki University Hospital - Helsinki (Finland), [3]Wenckebach Institute, University of Groningen, University Medical Center Groningen - Groningen (Netherlands), [4]Department of Otorhinolaryngology, Amsterdam University Medical Center, University of Amsterdam - Amsterdam (Netherlands)

Background / Objectives

Recurrent respiratory papillomatosis (RRP) is a disease with a high disease burden. Few studies have assessed quality of life (QoL) of RRP patients. The presented studies compares QoL of these patients with controls. Associations between QoL and sociodemographic and illness-related factors are examined, as is uptake of psychosocial care and speech therapy. Furthermore, a screening tool for psychosocial problems is presented.

Results

Ninety-one RRP patients (response = 67%) from the departments of otorhinolaryngology-head and neck surgery of the University Medical Center Groningen, Netherlands, and Helsinki University Hospital, Finland, completed the following patient reported outcome measures: hospital anxiety and depression scale (HADS), 15-dimensional health-related quality-of-life scale (15D), Voice Handicap Index (VHI) and the RAND 36-item health-related quality-of-life survey instrument, assessing health-related QoL and voice handicap, and they provided sociodemographic, illness-related characteristics, and allied healthcare use. The study population is described and differences between control groups are presented. The HADS was used as the gold standard to validate the Distress Thermometer & Problem List (DT&PL). The discriminative power, predictive value, internal consistency and predictive factors are described.

Conclusion

RRP patients had significantly higher mean scores on depression, health-related QoL (15D) and on voice problems (VHI), and significantly lower mean scores on anxiety than controls. Dutch patients had more pain and a decreased general health perception (RAND-36) than controls. Dutch patients and older patients were more depressed, women were more anxious, older patients had lower health-related QoL, and smoking was significantly associated with voice handicap. Patients who had received psychosocial care had significantly higher HADS-depression mean scores than patients who did not receive psychosocial care.
Analyzing the DT&PL, a DT cutoff score ≥4 gave the best sensitivity and specificity. Thirty-one percent of patients had significant distress according to the DT cutoff. Significantly more patients with a score above than under the cutoff had a referral wish. The PL was reliable. Patients' opinions on the DT&PL were largely favorable.

References

Having RRP has significant effect on voice-related QoL and depression, but has no negative effect on anxiety and health-related QoL. Risk factors for decreased functioning are different than previously hypothesized by many authors.
The Dutch and Finnish versions of the DT&PL are valid, reliable screening tools to find patients with distress.

HEAD AND NECK FORUM

HN4. Free Communications 1

00263

Opportunistic oral HPV infections in HIV/AIDS: Primary human three-dimensional tissue treated with HIV Protease Inhibitors is permissive to HPV16 infection and progeny virion biosynthesis

03. Pathogenesis

C. Meyers, S.D. Kang, S. Chatterjee, J. Biryukov, J. Milici, A.C. Salzberg, H. Chen, S. Alam

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Background / Objectives

Since the introduction of Highly Active Anti-Retroviral Therapy (HAART), rates of the AIDS-defining cervical cancer has decreased, but non-AIDS-defining oropharyngeal cancer has increased, in HIV/AIDS patients. Opportunistic HPV infections manifest as oral warts. HAART cytotoxicity manifests as adverse off-target damage of the mucosal epithelium, potentially exposing underlying tissue to infection by HPVs, and incidence of oral disease.

Results

We treated three-dimensional oral epithelial organotypic cultures with anti-retroviral protease inhibitors, then infected the tissues with authentic HPV16 virus. Following infection we assayed for infection by measuring the E1^E4 viral transcript expression and for the presence of newly sythesized infectious viral particles. We developed a protocol for BrdU labeling of authentic HPV16 propagating in full-thickness epithelium. Following BrdU labeling we visualized infection of keratinocytes by co-localizing BrdU labeled viral genomes with the HPV16 major capsid protein L1 using confocal microscopy.

Conclusion

In our study, anti-retroviral protease inhibitor treated primary human gingiva and cervical tissues were more sensitive to HPV16 infection compared to controls, as detected using the HPV16 E1^E4 transcript. Infectivity of progeny virion was associated with capsid maturation that correlated with extended time in culture. We were able to demonstrate *de novo* HPV16 synthesized progeny virus in the protease

inhibitor treated tissues using our BrdU labeling protocol and an anti-L1 monoclonal antibody using confocal microscopy.

References

Our studies present first time data that show infection of three-dimensional epithelial tissue with authentic HPV16 virus, as well as labeling of capsid/genome complexes of newly synthesized virions. Microarray analysis shows that Amprenavir treatment differentially regulated expression of multiple gene networks and signaling pathways that support virus biosynthesis. Increased viral load determines viral persistence and potential progression to head-and-neck cancers in patients undergoing HAART treatment. Critical to this process is the identification of mechanisms of HPV infection/trafficking in relation to tissue damage, that synergize with signaling pathways activated upon drug metabolism in oral epithelium.

00068

Vaccination in Recurrent Respiratory Papillomatosis

06. HPV therapeutic vaccines

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Background / Objectives

Anti-HPV vaccination has been debated frequently in both news and social media. A prophylactic anti-HPV vaccine in adolescents has been introduced in several countries that impact the incidence of HPV-related diseases. The clinical course of Recurrent Respiratory Papillomatosis varies, as some patients require only one or a few treatments in a lifetime, while others need several treatments a month for many years. The aim of this study was to estimate the effect of therapeutic HPV vaccination on RRP by conducting a meta-analysis.

Results

Publications with original data of at least five patients with RRP treated with HPV vaccination were included in the systematic review. To be included in the meta-analysis, publications had to provide individual data of number of surgeries and duration of observation period before and after vaccination. Available data on the number of surgeries and the duration of observation period before and after vaccination were extracted for calculation of the comparable intervals between surgeries. The length of follow-up for each patient was divided by the number of surgeries to identify the average time interval between surgeries.

Conclusion

The publications were analyzed as full text and their quality was assessed according to the SIGN recommendations. Six publications met all eligibility criteria and were included in the review. A meta-analysis was conducted for each of the independent variables; interval between operations before and after vaccination, gender, RRP onset (juvenile-onset RRP or adult-onset RRP), and HPV subtype. The meta-analysis indicates that HPV vaccination in fact prolongs the interval between surgeries with an overall SMD of 0.99 (95% CI: 0.59-1.40), independent of gender, RRP onset, and HPV subtype.

References

This study strengthens the idea that HPV vaccination has a positive effect on the course of the disease, which is of highly clinical relevance for both patients and surgeons. Seen through the light of the public debate of HPV vaccination, the results of the present study are particularly important as they support continued use of the vaccination.

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00049

CORRELATION BETWEEN SURVIVAL RATE AND MORTALITY AND THE PRESENCE OF THE HPV IN PATIENTS WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

08. HPV testing

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Background / Objectives

The Esophageal Squamous Cell Carcinoma (ESCC) is a carcinoma with high prevalence in world population[(1)]. Nowadays, the persistent infection by the HPV has been related in some geographical regions as a risk factor for the disease[(2,3)]. The HPV infection results in the immunoexpression of the p16 protein, which is being used as a marker of its oncogenic lineage [(4)]. The lack of global casuistic relating the ESCC and the survival rate and mortality in relation with the presence of the HPV encouraged us to develop this research. Our objectives consist in analyzing epidemiological aspects (age, gender, tumor grade, ulceration, invasion of the tumor) of the patients diagnosed with ESCC, and relate them with the prevalence of the HPV infection by p16 immunostainig.

Results

Electronic charts data of esophagectomies and esophagus biopsies made in the Evangelical University Hospital of Curitiba with pathological diagnostic of ESCC were reviewed and its samples reanalyzed. 58 cases were reviewed, diagnosed between January 2010 and January 2017, seeking the patients epidemiological profile, and the samples submitted to pathological and p16 immunohistochemical analysis. To analyze the mortality, by the way, 18 patients were excluded of our sample due to loss of clinical monitoring. To analyze the survival rate, more 5 were excluded to exactly calculate the time until patient's death. All the statistics were made using the chi-squared test and the ANOVA test.

Conclusion

Of the 58 analyzed cases, 40 were male (68.7%) and 18 were female (31,3%), with an average age of 63.2 years. p16 immunoexpression was 46.55% of our sample. A clinic-pathological correlation between p16 positivity and age, gender, tumor grade, ulceration and invasion has shown no evidence of significant statistical correlation

(respectively: p=0.5135, p=0.3564, p=0.6388, p=0.4298, p= 0.4517). The correlation between p16 positivity and mortality and the survival rate has also shown no significant statistical correlation (p=0.7195, p=0.3588).

References

The study revealed a high prevalence of HPV infection in our sample, being present in 46.55% of the cases. The epidemiological profile showed that the ESCC predominated in the masculine gender, with 63.2 years of average age. There was no evidence of significant statistical correlation between the survival rate ant mortality with the HPV presence. These data might be justified by the advanced stage of the disease that the patients come to our Hospital in the moment of the diagnostic, by the high aggressiveness of this carcinoma and the need of more cases for our sample. Due to the high prevalence noted in our study, it is indicative that this virus may play a role in the tumoral genesis of these tumors at this location and further researches are needed to establish it.

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00069

ORAL CANCER SCREENING. BRUSH SAMPLING AND FTA CARDS FOR AUTOMATED HR-HPV DIAGNOSIS AND AUTOMATED CYTOLOGY ANALYSES WITH AI OF MUCOSAL LESIONS

26. Oral HPV infection

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Background / Objectives

Oral cancer accounts for about 800-1000 new cases yearly in Sweden and the ratio of cancer related to high-risk human papillomavirus (HR-HPV) is increasing in the younger population due to changes in sexual habits. The most two frequent HR-HPV types 16 and 18 have both significant oncogenic potential.

Results

In this pilot study we evaluate two non-invasive automated methods; 1) detection of HR-HPV using FTA cards, and 2) image scanning of cytology for detection of potentially malignant lesions as well as eradicate the early stage of neoplasia.

160 patients with verified HR-HPV oropharyngeal cancer, previous ano-genital HR-HPV-infection or potentially malignant oral disorder were recruited for non-invasive brush sampling and analyzed with two validated automated methods both used in cervix cancer screening. For analysis of HR-HPV DNA the indicating FTA elute micro cardTM were used for dry collection, transportation and storage of the brush samples. For analysis of cell morphology changes an automated liquid base Cytology method (Preserve Cyt) combined with deep learning computer aided technique was used.

Conclusion

Results: Preliminary results show that the FTA-method is reliable and that separation of healthy and malignant cells is possible by scanning with AI.

References

With further development of these fully automated methods, it is possible to implement a National Screening Program of the oral mucosa, and thereby select patients for further investigation in order to find lesions with potential malignancy in an early stage.

00368

THE INCIDENCE OF ORAL HUMAN PAPILLOMAVIRUS INFECTION WITHIN THE HEALTHY YOUNG ADULT UK POPULATION

26. Oral HPV infection

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Background / Objectives

The incidence of oropharyngeal squamous cell carcinoma (OSCC) cases in the UK has doubled within the last 15 years [1]. Despite the traditional link between the development of OSCCs and engagement with riskier lifestyle choices such as heavy alcohol consumption and smoking, emerging research suggests that possessing an active oral HPV infection can also lead to OSCC progression. Currently, more than 50% of OSCC cases in the UK are estimated to be HPV-positive [1]; 90% of which are HPV-16 type-specific [2], with the majority diagnosed in young adult males [3]. However, oral HPV infection rates, genotype incidence, and viral load within the healthy adult UK population are unknown, making identification of populations that are at risk of developing OSCCs more difficult. As such, this investigation aimed to establish oral HPV infection rates within a representative young adult UK population of males and females to determine if incidence of infection is influenced by vaccination status, oral locality, and/or lifestyle choices of an individual.

Results

To detect the presence of HPV DNA in the oral cavity, we established a novel, reproducible, and highly-sensitive real-time polymerase chain reaction (RT-PCR) technique. Consensus MY09/11 primers were used to detect the L1 gene across multiple HPV genotypes, the products of which were examined by RT-PCR dissociation curves allowing identification of positive samples. These samples were then further screened for the genotypes targeted by the quadrivalent vaccine (HPV-6, -11, -16 and -18) by quantitative RT-PCR to determine viral type and load.

A total of 438 participants were recruited and donated oral mucosal cell samples. The majority were aged between 18-25 years old and lived in the East Midlands region of the UK. Genomic DNA was extracted from the samples (Males n=178; Females

n=260) and screened as described to determine oral HPV infection rates, genotype prevalence, and viral load. Participants also completed a questionnaire consisting of questions on socio-demographics, lifestyle choices, sexual behaviour, and HPV vaccination status. Statistical regression analyses will determine correlations between riskier behaviours and/or vaccination status, and oral HPV incidence data.

References

The expected results of the study will describe the incidence of oral HPV infections within the young adult UK population, allowing assessment of whether there are differences in the frequency of incidence and viral load between 1) UK-based young adult males and females, 2) vaccinated and non-vaccinated individuals, 3) those who exhibit riskier behaviours and those who do not. As such, this study will ultimately identify populations at risk of developing HPV-positive OSCCs, and thereby inform HPV-positive OSCC prevention strategies.

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00393

Prevalence of oral and cervical human papillomavirus infections in women attending colposcopy clinics in Ireland

26. Oral HPV infection

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Background / Objectives

HPV has been recently recognised as one of the primary causes of Oropharyngeal squamous cell cancers (OSSCs). Despite the recognised role of HPV in OSSCs, the epidemiology of oral HPV infection is not well understood. The natural history of oral HPV infections and the risk factors for persistent HPV infection in the oropharynx may differ from cervical HPV infection. There is currently limited data available on oral HPV incidence, persistence and clearance in healthy individuals in the Irish population.

Results

A prospective observational cohort study was undertaken on selected at-risk populations which comprises of women with high grade CIN attending the Colposcopy units at The Coombe Women and Infants University Hospital and the AMNCH Hospital, Dublin, Ireland.

An oral rinse sample was taken from the women referred with high grade CIN at the baseline visit following informed written consent. HPV testing was carried out on the Cobas 4800 platform with the Cobas HPV DNA test and where oral samples tested positive, a concurrent cervical biopsy/LLETZ treatment sample from the same patient was also tested. All positive samples were genotyped with the INNOLIPA HPV genotyping assay

Questionnaires were also administered to all participants to assess socio-demographic characteristics, sexual and contraceptive history, alcohol and tobacco use, and relevant clinical history.

Conclusion

227 women were tested for oral HPV of which 10% were positive. Majority of the positive samples were HPV 18 positive followed by Other Risk types (OR) in 5.0% of samples. The cervical and oral samples displayed concurrent genotypes in 28.0% of cases.

References

We observed a high prevalence of oral HPV infections in women referred with high grade CIN. Concurrent oral and cervical HPV infections were present in one fourth of the study population.

00086

HUMAN PAPILLOMAVIRUS IN CARCINOMAS OF THE SINONASAL TRACT

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

High-risk HPV (HR HPV) is an established causative factor for oropharyngeal carcinomas, but in recent times there has been increasing evidence of the role for HPV in non-oropharyngeal head and neck cancers including those arising in the sinonasal tract. However, the prevalence and clinical significance of HPV-associated sinonasal cancer are poorly understood. This study aims to determine the prevalence of HR HPV infection in a cohort of sinonasal carcinomas (SNC) and whether this status impacts overall patient survival.

Results

132 patients diagnosed with sinonasal carcinoma between October 2000 and March 2018 were identified from the pathology archive of a single UK tertiary referral centre. Residual tissue was available for testing for 124 cases, where p16 immunohistochemistry was performed and, if positive, DNA in situ hybridisation for HR HPV types was undertaken. Molecular genotyping using a PCR and luminex based strategy was also performed on a representative sub-cohort. Overall survival was determined from electronic patient records.

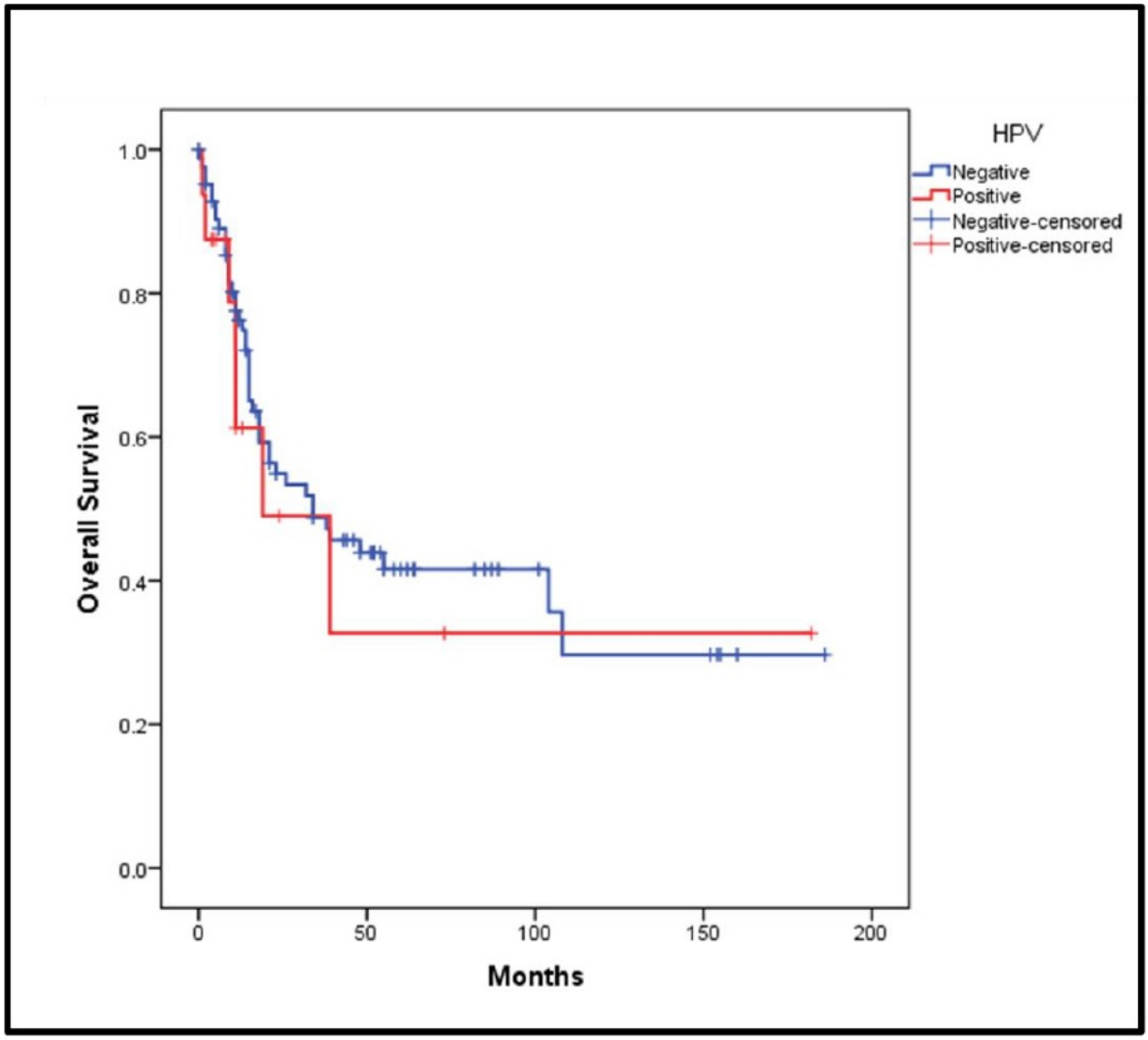
Conclusion

Of the 132 cases, 124 sinonasal carcinomas were available for HPV testing. 14% were positive for p16 and HR HPV DNA by in situ hybridization. All of these cases showed strong reactivity for p16 immunohistochemistry. The HPV-related carcinomas occurred in 12 men and 5 women with an age range of 29 to 82 (Mean. 53 y). They consisted of 11 squamous cell carcinomas (including one papillary type), and one each of small cell neuroendocrine carcinoma, adenoid cystic carcinoma, and

adenocarcinoma. A further 3 HPV positive carcinomas were difficult to classify according to current histopathological criteria. Follow up data was retrievable for 100 patients (including 16 HR-HPV positive). Kaplan-Meier plot for overall survival outcome is demonstrated in the figure below. There was no significant difference in overall survival between the patients with HPV positive and negative carcinomas (Chi square 0.267, p=0.605).

References

We show that HR HPV is associated with a significant proportion of SNCs which, to our knowledge is the first report of its kind from the United Kingdom. Unlike HPV-associated oropharyngeal carcinomas, HPV positive SNCs appear to show wide phenotypic variation including squamous, salivary, neuroendocrine and adeno-carcinomas. While other groups have shown a tendency to improved survival, HR HPV infection in SNC did not confer a survival advantage in our series. However, further work is necessary to determine the full clinical significance of HPV in SNC due to the rarity of this disease, low cohort numbers and the effect of geographic and phenotypic diversity.


HPV
Negative
Positive
Negative-censored
Positive-censored
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Months

00169

PREVALENCE OF BIOLOGICALLY ACTIVE HPV INFECTION IN TUMOR-FREE OROPHARYNGEAL TISSUE OF OPSCC-PATIENTS.

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Oncogenically active infection with high risk types of human papillomavirus (HR-HPV) represents an established risk factor for development of oropharyngeal squamous cell carcinoma (OPSCC) [1]. Similar to cervical cancer, persistent HR-HPV infection of the oropharyngeal mucosa might be a precursor to cancer and be responsible for field cancerization as well as higher local recurrence rates in patients with an HPV-driven OPSCC [2]. Thereafter, early detection of persistent HR-HPV infection in tumor-free tissue can be relevant for disease surveillance. The aim of the study was to investigate in OPSCC patients the prevalence of HR-HPV infection in tumors, normal appearing mucosa adjacent to the tumor and in distant mucosa.

Results

From 11/09 to 04/12 47 patients (36 males and 11 female, range 30-81y) undergoing panendoscopy for evaluation of an untreated OPSCC were prospectively enrolled. Tumor specimens as well as biopsies of normal appearing mucosa adjacent to the tumor and mucosa of the contralateral tonsil were examined for HPV-DNA by BSGP5+/6+ PCR/MPG and E6*I mRNA. $p16^{INK4A}$ immunohistochemistry and histopathological examination were performed too. To avoid cross-contamination instruments were replaced after each biopsy. Prevalence of HPV-DNA, HPV-RNA and $p16^{INK4A}$ overexpression in normal mucosa were evaluated in comparison to tumor HPV-status.

Conclusion

Of 47 tumor samples 24 (51%) were concurrently positive for HR-HPV-DNA and $p16^{INK4A}$ (21 HPV16, 3 HPV33) and 21 (44%) for HPV-mRNA (18 HPV16; 3 HPV33). Among the 24 cases showing HPV-DNA + $p16^{INK4A}$ positivity in tumor, 9 samples (38%) of mucosa adjacent to the tumor were positive for HPV-DNA, but only 1 (4%) for HPV-RNA. In distant mucosa, 5 samples (21%) were positive for HPV-DNA. In none of the samples of the contralateral tonsil, HPV-RNA was detected.

References

Very small evidence was found for transcriptionally active HPV-Infection in normal appearing mucosa adjacent to the tumor and in contralateral tonsil tissue of OPSCC-patients. In fact, HPV-E6*I mRNA, which strongly indicates the oncogenic role of HPV in tumor, was detected in only one sample. Moreover, HPV-DNA detection alone still remains not conclusive, considering its lack of tumor specificity [3]. The absence of HPV-infected tissues outside the tumor itself support the clinical observation that patients with HPV-driven OPSCC have lower risk of recurrence and developing second primary malignancies [4].

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00204

EPIDEMIOLOGY OF OROPHARYNGEAL CANCER RELATED TO HUMAN PAPILLOMAVIRUS IN A CLASSICALLY LOW BURDEN REGION

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papillomavirus (HPV)-related oropharyngeal cancer is a well-established increasing epidemic in some regions of the world such as North America and Northern Europe. Yet, the epidemiology of the disease in Southern Europe has not been extensively investigated.

Results

We conducted a retrospective cohort study of patients diagnosed with a primary oropharyngeal cancer in four hospitals of Catalonia from 1991 to 2017. Formalin-fixed, paraffin-embedded cancer tissues were subject to histopathological evaluation, DNA quality control, HPV-DNA detection and p16INK4a immunohistochemistry. Sociodemographic and clinical data was collected from medical records. Multivariate Bayesian models were used to evaluate factors associated with HPV positivity as defined by double positivity for HPV-DNA/p16INK4a, overall and by anatomical subsite. Specific time trends analyses were also conducted.

Conclusion

A total of 864 patients yielded a valid HPV-DNA result. The adjusted prevalence of HPV-related cases was 9.7% considering double positivity for HPV-DNA/p16INK4a (78/864). HPV-related patients were significantly more likely to be non-smokers, non-drinkers, having a tonsillar carcinoma or diagnosed at advanced stages. Some associations were not observed for all oropharyngeal anatomical subsites or when only considering cases p16INK4a positive. In the specific time trends analysis, an increasing risk of being a HPV-related oropharyngeal cancer was observed at most recent periods (five-years period increase of 33% during 1993-2017). This increase was highest (170%) and statistically significant only at most recent years (2013-2017).

References

Our results provide a comprehensive assessment of the epidemiological landscape of the HPV-related oropharyngeal cancer in a region of Southern Europe and indicate that the disease epidemic has started to sharply increase in the most recent years in our setting as it happened two decades ago in areas where nowadays most oropharyngeal cancer cases are HPV related.

00222

A SYSTEMATIC REVIEW OF THE HPV-ATTRIBUTABLE FRACTION OF OROPHARYNGEAL SQUAMOUS CELL CANCERS IN GERMANY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Wide variations in the proportion of oropharyngeal squamous cell cancers (OPSCC) attributable to HPV have been reported. The objective of the present study was to summarize the HPV-attributable fraction (HPV-AF) of OPSCC in Germany as a source for future estimations of HPV disease burden.

Results

A systematic literature review was conducted in Medline and Embase. Inclusion criteria were 1) patients with SCC localized in the oropharynx (or oropharyngeal sublocations such as tonsil), 2) treated at a German medical center and 3) results of HPV DNA PCR combined with p16INK4a immunohistochemistry were reported to determine the HPV status.

Conclusion

Out of 287 screened publications, 14 were identified that fulfilled the inclusion criteria. The HPV-AF in OPSCC varied considerably between the individual studies ranging from 11.5% (12/104, Frankfurt, diagnosis between 1988-2008) to 47.5% (28/59, Münster, <2013). Two of the included studies did not only provide the HPV-AF for the entire observed calendar period, but also for separate years, allowing to more accurately assess changes over time. Giessen (n=599) reported an HPV-AF of 21% in 2000 and of 53% in 2015, with an average increase of 1.6% per year. Berlin

(n=227) reported a similar increase, with an HPV-AF of 38% in 2004 and 71% in 2013.

References

Reported HPV prevalence in OPSCC in Germany varies widely. Single studies including patients diagnosed after 2012 point towards an HPV-attributable fraction in OPSCC of >50% in Germany.

00493

INCIDENCE TRENDS IN HUMAN PAPILLOMAVIRUS (HPV)-ASSOCIATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA SUBSITES IN THE UNITED STATES AND CANADA, 1995-2015

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

The incidence of human papillomavirus (HPV)-associated head and neck (oropharyngeal) cancer has increased dramatically in the United States in the last three decades, and it is currently the leading HPV-associated cancer. No previous studies have described the incidence trends among the oropharyngeal cancer subsites that are most associated with HPV. We aimed to describe incidence trends in HPV-associated oropharyngeal squamous cell carcinoma in the United States and Canada by oropharyngeal subsites.

Results

Age-adjusted incidence rates of HPV-associated oropharyngeal cancer were calculated from the North American Association for Central Cancer Registries (NAACCR) database (1995-2015) covering the United States and Canada. Rates were stratified by anatomic subsites (palatine tonsil, base of tongue, lingual tonsil, soft palate/uvula, oropharynx proper, and pharynx), and presented per 100,000 person-years (PY). Overall rates for the entire study period, rate ratios (RR), and percent changes (PC) comparing the 1995 rate and 2015 rate were calculated for each subsite. Joinpoint regression estimated increases/decreases in age-adjusted incidence over time for each subsite through average annual percent changes (AAPC).

Conclusion

There were 271,223 cases in our cohort; predominantly males (79%), and non-Hispanic whites (78%). Most common oropharyngeal subsites were palatine tonsil (41%) and base of tongue (35%). The overall incidence was 4.10 per 100,000 PY with an AAPC of 2.28 ($p < 0.01$). Overall, age-adjusted incidence rate increased by 53% from 1995-2015 (3.19 per 100,000 PY in 1995, and 4.90 per 100,000 PY in 2015). Patients with palatine tonsil (AAPC=3.30), base of tongue (AAPC=3.10), and oropharynx proper (AAPC=1.70) experienced significant rate increases from 1995-2015 ($p<0.01$), while rates decreased for soft palate/uvula (AAPC=-3.27, $p < 0.01$). Rates remained stable for lingual tonsil and pharynx. Palatine tonsil also had the highest incidence rate from 1995-2015 (1.67 per 100,000 PY), followed by base of tongue (1.43 per 100,000 PY), and oropharynx proper (0.42 per 100,000 PY). Compared with palatine tonsil, all other oropharyngeal subsites had significantly lower rates (RR range=0.07-0.86, $p < 0.05$).

References

In the United States and Canada, the incidence of HPV-associated oropharyngeal cancer has increased by more than 50% in the last two decades, especially in the palatine tonsil and base of tongue. There is need for targeted primary prevention efforts to decrease the ever-increasing incidence of HPV-associated oropharyngeal cancer.

References

00526

TYPE-SPECIFIC DATA ON HUMAN PAPILLOMAVIRUS INFECTION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA IN EUROPE

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

To assess availability of recent type-specific data on human papillomavirus (HPV) infection in oropharyngeal squamous cell carcinoma (OPSCC) and report on type-specific HPV prevalence in OPSCC in Europe.

Results

PubMed/Medline and EMBASE databases were systematically searched for full publications reporting type-specific HPV DNA detection in histologically confirmed OPSCC. Bibliographies were also searched. Original studies reporting on HPV 16 and 18 and ≥1 other high-risk type were included. Exclusion criteria: publication before 2012, not English, special populations (e.g., HIV-infected only), N<25. Key information, including study type, country, population characteristics, sample type, HPV assay, HPV types detected, p16INK4a expression, E6/E7 mRNA detection was extracted.

Conclusion

26 publications were included: 19 reporting data on OPSCC overall, 6 on tonsillar SCC, 5 on base of tongue SCC, and 3 studies on other OPSCC sites. Ten studies originated from Northern Europe, 8 from Western Europe, 6 from Southern Europe, 1 from Eastern Europe, and 1 study reported across European regions. Most studies originated from Italy (5), Germany and Sweden (4 each), and France (3). Across Europe, HPV was detected in 50.4% of 3,302 oropharyngeal SCC cases overall, 66.9% of 650 tonsillar SCC, and 59.3% of 275 base of tongue SCC cases. HPV 16

was detected in 88% of HPV-positive OPSCC and was the dominant type across all subsites.

References

There is a growing body of evidence on HPV in OPSCC in Europe. HPV is detected in over half of all European OPSCC cases; the predominant type is HPV 16 across all subsites investigated.

HEAD AND NECK FORUM

HN5. Free Communications 2

00030

HPV IN BENIGN AND MALIGNANT HEAD AND NECK PATHOLOGY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papillomavirus is one of the most common agents related with sexually transmitted diseases around the world. Its oncogenic role in cervical cancer is well established, however, a number of benign and malignant conditions in Otolaryngology practice are also related to this agent.

In particular, recurrent respiratory papillomatosis (RRP), caused by HPV 6 and 11, is characterized by growth of multiple papillomas arising from the larynx and can manifest in early childhood or in adulthood; on the other hand, HPV infection has assumed a pivotal role in the growing incidence of oropharyngeal squamous-cell carcinoma.

Results

We performed a retrospective analysis of patients with RRP diagnosed in the Otolaryngology Department of CHVNG/E from December/2010 and December/2017, as well as a retrospective analysis of oropharyngeal tumours detected in our department between January/2014 and December/2017 and studied their clinical characteristics.

Conclusion

Seven patients with RRP were diagnosed (57% male, mean age at diagnosis of 52 years), with history of tobacco abuse in 71% (n=5) of cases. The leading symptom was dysphonia in 86% (n=6), with evidence of a single papilloma in 57% (n=4) of patients, mainly located in the glottis. All patients were submitted to surgical treatment, with recurrence in three patients and malignant transformation in one patient.

Forty-four cases of squamous-cell oropharyngeal carcinoma were included (91% male, mean age 57 years), with history of alchool or tobacco abuse in 82% (n=36). The most prevalent initial symptom was odynophagia in 68% (n=30) and cervical mass in 14% (n=6) of patients. The majority of tumours presented in advanced stages (IVa or IVb in 77%), and were submitted to treatment with chemoradiotherapy in 68% (n=30) or surgery in 14% (n=6). Detection of HPV using p16 immunohistochemistry was performed in eight cases, with one positive tumour.

References

Although a benign disease, RRP presents an unpredictable nature and tendency to recur and spread in the respiratory tract, as well as a risk of malignant conversion.

The global increase in incidence of oropharyngeal cancer, particularly in younger patients without exposure to traditional risk factors, underlines the importance of HPV in the epidemiology of this disease.

The detection of HPV status must be included in the diagnostic work-up of an oropharyngeal tumour, due to its relevant implications in prognosis, which was been recognized in the most recent update of AJCC staging system.

00079

The use of HPV16-E5, EGFR and pEGFR as prognostic biomarkers for oropharyngeal cancer patients.

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Anti-EGFR therapies in combination with radiotherapy are being studied on de-escalation clinical trials for HPV-related oropharyngeal cancer (OPC) patients. The HPV16-E5 oncoprotein increases recycling of activated EGFR to the cell surface, enhancing factor signal transduction. Our aim was to evaluate viral HPV16-E5 oncogene expression as well as EGFR and pEGFR, protein levels as biomarkers for clinical outcome in a retrospective cohort of OPC patients.

Results

Formalin-fixed-paraffin-embedded OPC were collected. OPC samples containing HPV-DNA were subject to viral E6*I mRNA detection and $p16^{INK4a}$ immunohistochemistry (IHC). HPV16-positive cases were evaluated for HPV16-E5 (RT-PCR) and EGFR/pEGFR (IHC). A stratified random sample of HPV-negative samples was evaluated for EGFR/pEGFR. Overall survival (OS) and disease free survival (DFS) estimates were assessed.

Conclusion

Among the 788 OPC patient samples, 54 where double positive for HPV16-DNA/p16^{INK4a}. HPV16-E5 expression was found in 41 samples (77.4%). EGFR expression was observed in 37.7% vs 70.8% in HPV16-positive and HPV-negative samples, respectively; (adjusted OR 0.15 [0.04-0.56 95%). Expression of pEGFR followed an inverse pattern with 39.6% and 24.9% detection in HPV16-positive and HPV-negative samples; (adjusted OR 1.58 [0.48-5.17]). Within HPV16-positive cases, no association between HPV16-E5/EGFR nor pEGFR was observed.The combination of HPV status and EGFR or pEGFR expression were predictors of OS and DFS.

References

HPV16-E5 is highly expressed on HPV16-positive OPCs. Interestingly, HPV16-positive cases expressed significantly more pEGFR while HPV-negative cases expressed more EGFR. The combinations of HPV status and EGFR or pEGFR are useful biomarkers for prognosis outcome in OPC patients.

00090

MINIMALLY INVASIVE DUAL TESTING FOR ACTIVE HPV E6/E7 AND PD-L1 EXPRESSION IN OROPHARYNGEAL CANCER

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

HPV-status and PD-L1expression level are important biomarkers in oropharyngeal cancers (OPC). Trials assessing new treatment options for HPV-driven OPC, including PD1/PDL1 inhibitors are ongoing. Studies have outlined that detection of HPV-DNA in oral rinses of patients with HPV-driven OPC after treatment completion is associated with an increased risk of disease recurrence. Biomarkers more specific than HPV-DNA to HPV-driven oncogenic process, such as E6/E7 mRNA, may be more useful to track residual disease and/or recurrence after treatment. In this proof of concept study, we conducted a dual biomarker assay to measure both PD-L1 and E6, E7 mRNA overexpression simultaneously on oral swab samples from a cohort of OPC with defined HPV and PD-L1 status by IHC.

Results

Forty patients with oropharyngeal squamous cell carcinoma (OPSCC) at Gustave Roussy Cancer Center, were enrolled after protocol approval by the Institutional Review Board and patient written informed consent. Swabs and biopsies were collected from the same patient lesion. Biopsies were preserved as FFPE tumor tissue blocks and swabs collected into proprietary fixative for analysis by flow cytometry (flow). Determination of HPV status by current practice of p16 IHC and positive confirmation by HPV-DNA ISH was performed by Gustave Roussy. Additional anti-PD-L1 (clone 28–8) IHC staining was performed by BioReference Laboratories and analyzed by Gustave Roussy for PD-L1 status. Dual PD-L1 & E6, E7 mRNA testing by flow at IncellDx occurred on 1mL fixed oral swab samples. Samples were prepared by 35µm nylon mesh straining and washes. ISH with a HPV E6, E7 mRNA probe occurred followed by stringency washes. Samples were then blocked with BSA and stained with anti PD-L1 antibody (clone 28-8). Lastly, a cell

cycle dye was applied, and the samples were analyzed for expression on a CytoFLEX flow cytometer (Beckman Coulter). Samples with a minimum 1,000 nucleated cells were included in this dataset (38).

Conclusion

Performance E6,E7 mRNA vs p16	Result
Sensitivity	67% (10/15)
Specificity	65% (15/23)
PPV	56%
NPV	75%
Concordance	66% (25/38)

Performance PD-L1 Flow vs IHC	Result
Sensitivity	20% (3/15)
Specificity	90% (18/20)
PPV	60%
NPV	60%
Concordance	60% (21/35)

*PD-L1 IHC reported as positive when there was at least 1% positive staining.

References

HPV E6,E7 mRNA and PD-L1 are detectable in salivary samples which paves the way for use of this sample type in clinical applications. Improvement of the probe design could increase the concordance rate between FFPE and swabs outcomes. Correlation of PD-L1 result by IHC and that of flow cytometry needs further investigation; a 1% cut off for IHC may not be a relevant cut off for comparison to flow cytometry, leading to the low sensitivity reported here.

00167

SEX DIFFERENCES IN HPV IMMUNITY AMONG ADULTS WITHOUT CANCER

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

The incidence of human papillomavirus (HPV) -associated head and neck cancer is rising in North America. Among men, the incidence is more than twice than that of women, although the prevalence of cancers attributable to HPV is increasing among both sexes. How sexual exposure and sex-specific immune response to HPV contribute to the difference in cancer incidence is unclear. The objective of this study is to determine whether the observed epidemiological sex difference is explained by differences in sexual exposure and/or by immune response.

Results

In a multi-institutional, cross-sectional study, peripheral blood and behavioral data was collected from 374 adult patients without cancer seeking care at outpatient clinics. Seroprevalence of antibodies to HPV L1 capsid antigen was compared by demographic and behavioral characteristics.

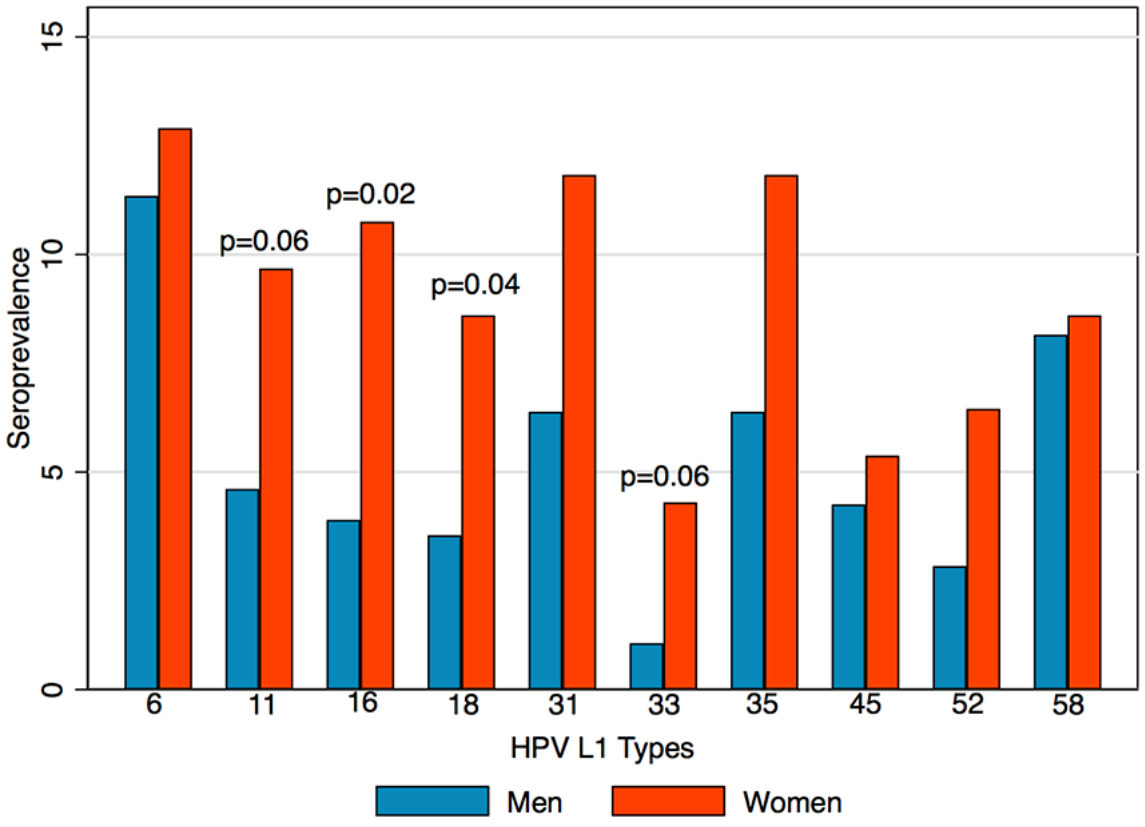
Conclusion

A significantly higher seroprevalence among women compared with men was observed for HPV16 (OR=2.96, 95% CI=1.21-7.21) and HPV18 (OR=2.84, 95% CI=1.06-7.60) L1 antibodies (Figure 1). This difference persisted for HPV16 L1 seroprevalence after controlling for lifetime and recent sexual behavior. Higher numbers of lifetime and recent oral sexual partners were both associated with increased odds of HPV16 (lifetime OR=1.05, 95% CI=1.01-1.08; recent OR=1.54, 95% CI=1.15-2.07) and with HPV18 (lifetime OR=1.04, 95% CI=1.01-1.08; recent OR=1.40, 95% CI=1.07-1.82) L1 seroprevalence after controlling for sex. In contrast, the number of vaginal sexual partners was not associated with HPV16 (lifetime

OR=1.00, 95% CI=0.96-1.05; recent OR=0.91, 95% CI=0.37-2.24) or HPV18 (lifetime OR=1.00, 95% CI=0.96-1.05; recent OR=0.76, 95% CI 0.28-2.07) L1 seroprevalence.

References

These findings suggest a more robust immune response to HPV16 and HPV18 L1 seroprevalence among women compared with men that is not explained by differences in sexual behavior. An increased number of oral sexual partners, rather than vaginal, is independently associated with a higher HPV16 and HPV18 L1 seroprevalence, supporting a possible role for site of mucosal exposure in the HPV immune response.



00183

Survival Rates for Patients With Barrett High-Grade Dysplasia and Esophageal Adenocarcinoma With or Without Human Papillomavirus Infection

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

High-risk (hr)-human papillomavirus (HPV) has been associated with Barrett dysplasia and oesophageal adenocarcinoma (OAC). Nevertheless, the prognostic significance of esophageal tumour HPV status is unknown.

Results

We hypothesized that HPV associated esophageal tumors would show a favourable prognosis (as in viral positive head and neck cancers). Thus, we studied the association between HPV and related biomarkers of high-grade dysplasia (HGD)/OAC and survival. Pre-treatment biopsies were used for HPV DNA determination via PCR, in-situ hybridization for E6/E7mRNA and immunohistochemistry for p16INK4A and p53. Sequencing of TP53 was also undertaken.

Design

Retrospective, case-control study.

Setting

Secondary and tertiary referral centres.

Participants

One hundred and fifty one patients were assessed for eligibility. Nine were excluded.

Main Outcomes and Measures

Disease-free survival (DFS) and overall survival (OS).

Conclusion

Amongst 142 HGD/EAC patients [M:F, 126(88.7%):16 (11.3%), mean age, 66.0 years, SD+/- 12.1], 37 were HPV+ and 105 HPV- . HPV+ patients were mostly p16ink4ahigh, p53low and wild-type TP53. There were more Tis/T1/T2 tumors in HPV+ subjects as compared with HPV- patients (75.7% versus 54.3%, p=0.02). Mean disease-free survival was superior in the HPV+ group (40.3 months versus 24.1 months, p=0.003) as was overall survival [43.7 months versus 29.8 months, p=0.009]. Recurrence/progression was much reduced in the HPV+ cohort (24.3% vs 58.1%, p=0.0004) as was distant metastasis (8.1% vs 27.6%, p=0.015) and death from EAC (13.5% versus 36.2%, p=0.01). HPV and transcriptionally active virus positivity were both associated with a superior DFS (HR=0.33; 95%CI: 0.16-0.67, p=0.002) and (HR=0.44; 95%CI: 0.22-0.88, p=0.02) respectively (log-rank test). E6/E7 mRNA positivity had borderline significance for improved DFS (HR=0.50; 95%CI: 0.24-1.05, p=0.069) but not p16INK4Ahigh or p53low. On multivariate analysis, superior DFS was demonstrated for HPV (HR=0.39, 95%CI; 0.18-0.85, p=0.02) biologically active virus (HR=0.36, 95%CI: 0.15-0.86, p=0.02), E6/E7mRNA (HR=0.36, 95%CI: 0.14-0.96, p=0.04) and p16high (HR=0.49, 95%CI: 0.27-0.89, p=0.02).

References

HPV+ HGD/EAC is a distinct biological entity with a favourable prognosis as compared with viral negative esophageal tumors. If these findings are confirmed in larger cohorts with more advanced disease, it presents an opportunity for treatment de-escalation in the hope of reducing toxicity without deleteriously affecting survival.

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00191

EFFECT OF COMORBIDITIES ON SURVIVAL IN HPV-RELATED AND -UNRELATED HEAD AND NECK CANCER SURVIVORS

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

The increasing incidence of human papillomavirus (HPV)-related head and neck cancer (HNC) has lead to increasing prevalence of survivors, yet prevalence of comorbidities during the survivorship period and their effects on survival are relatively unknown.

Results

In this retrospective cross-sectional study, individuals with a first incident primary diagnosis of HNC from 2004-2011 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked Databases were included in analysis and classified into HPV-related or HPV-unrelated HNC. The presence or absence of 30 different comorbid conditions of interest was identified. Association between comorbidity and overall survival was evaluated.

Conclusion

The study population consisted of 8,025 HPV-unrelated and 2,499 HPV-related HNC patients. Hypertension, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease were all highly prevalent at the time of cancer diagnosis and increased over time for both groups. These comorbidities were found at significantly lower rates in the HPV-related HNC population, yet in both groups were associated with increased risk of death. The probability of development of cancer-related comorbidities such as pneumonia, dysphagia, weight loss, malnutrition, and dental issues rose significantly in both groups following treatment but were more likely in HPV-related HNC. In both, the presence of each comorbidity either at diagnosis or during survivorship was associated with significantly increased risk of death.

References

There is a large burden of comorbidities in both HPV-related and HPV-unrelated HNC patients, which are associated with decreased survival. Oncologic surveillance should not be limited to disease status evaluation, but also screening for the highly prevalent conditions associated with risk of death.

00296

FEASIBILITY PILOT STUDY OF A HPV16/18 E6 ONCOPROTEIN TEST IN OROPHARYNGEAL AND UNKNOWN PRIMARY CANCERS

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

High-risk HPVs, in about 90% HPV16, are associated with a subset of head and neck cancers especially in the oropharynx and a substantial proportion of neck cancer of unknown primary (CUP), both with increasing trend. Patients with HPV-driven oropharyngeal carcinomas (OPC) and CUP were shown to have a better survival rate compared to HPV-negative ones. Current guidelines state that HPV status of OPC should be determined by HPV DNA detection and p16-IHC on histological material. To assess feasibility of fast testing of transforming HPV infection in diagnostic settings on cytological material, we are conducting a pilot study using a commercially available lateral-flow test for HPV 16/18 E6 oncoproteins, the OncoE6 test.

Results

We so far included 17 patients from Treviso and Trieste Hospital (Italy), diagnosed with CUP or OPC with neck node metastasis and with no prior history of cancer. We collected fine needle aspiration cytology (FNAC) samples from primary tumour and clinically assessed metastatic nodes and tested those for presence of HPV16/18 E6 oncoprotein using the OncoE6 test (Arbor Vita). Results were correlated with other HPV markers. As clinical routine, HPV-DNA and p16-IHC were tested on patients' biopsy or surgical specimen. Sera were collected at the time of diagnosis and tested by bead-based multiplex serology. HPV seropositivity was defined by high HPV16 E6 antibody levels (MFI>1000) or presence of type-concordant E6 and E7 antibodies of

other high-risk HPV types (18, 31, 33, 35, 45, 52, 58). HPV-driven tumours were defined by (1) positivity for HPV-DNA and p16 and/or (2) HPV-seropositivity.

Conclusion

Six (46%) of 13 OPC and 1(25%) of 4 CUP were HPV-driven. All FNAC samples from the 5 HPV16-driven OPC and 4 of the 5 corresponding metastatic lymph nodes and the HPV16-CUP were HPV16 E6 positive. All non-HPV-driven and the single HPV33-driven tumours were negative for HPV16 and HPV18 E6. Thus, the E6 protein assay had a sensitivity of 100% (95% CI: 46%-100%) for HPV16-driven OPC and a specificity of 100% (95% CI: 52%-100%) and sensitivity of 83% (95% CI: 36%-99%) for metastatic lymph node with a specificity of 100% (95% CI: 67%-100%).

References

In this pilot study, we found the OncoE6 test to be feasible in FNAC samples from OPC and node metastases, allowing clinicians to get fast and reliable HPV status information with a less invasive procedure. OncoE6 test can be run with minimal laboratory equipment in a “bed-side fashion” by not highly trained personnel. High concordance of OncoE6 results with standard HPV markers is encouraging. However, OncoE6 test specificity for HPV16/18 entails the risk of getting false negative results in tumours caused by other HPV types.

00304

ROLE OF VIRAL TRAITS IN PROGNOSIS OF HPV16-RELATED OROPHARYNGEAL CANCER PATIENTS

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Although HPV-related oropharyngeal cancer (OPC) patients show better prognosis than those non-related, around 20% fail to treatment and this population needs to be clearly identified. Our main aim was to explore the prognostic value of several viral characteristics such as genome physical status, variants lineage and viral load of HPV16 positive OPC patients.

Results

From a retrospective cohort of 868 OPC patients newly diagnosed from 1991 to 2017 in four hospitals from Catalonia (1), we selected those patients HPV16 positive after SPF10/LiPA25 detection. A total of 83 cases were included, and tested for HPV E6*I mRNA, p16INK4a, genome physical status (episomal vs integrated), variants lineages and viral load. SPF10/LiPA25, HPV E6*I mRNA, p16INK4a were performed as previously described (1). The integrated/episomal status of the viral genome was determined by amplifying HPV16 E2 gene assuming that integration of the viral genome most often concurs with loss of E2. Phylogenetic relationships of the amplified LCR-E6 region DNA sequences were estimated using an Evolutionary Placement Algorithm on RAxML v8.0.16 placing the DNA fragments into the HPV16 reference tree. We integrated the results for all nodes and used 0.7 as a likelihood cutoff value to classify each sample into a specific variant lineage, namely A1-3, A4, B, C or D. We employed a SYBR Green-based qPCR using a specific set of primers for HPV16 E6 gene to calculate viral load normalized according to the number of cells, as estimated using a qPCR for the cellular tubulin gene. Risk factors, clinical and follow-up data were collected from medical records.

Conclusion

From 83 HPV16 OPC cases-15.2% were integrated, 81.8% were assigned as linage A variants, and mean viral load value was 27578 copies per 10^3 cells. Bivariant analyses between cases characteristics and viral information revealed that all non-A variants showed double positivity for HPV DNA and p16INK4a, whereas p16INK4a positivity in A variants was detected in 75% of the cases (P=0.058). In Kaplan Meier curve analyses comparing variant and integration status and considering only HPV DNA and p16INK4a positive cases, A integrated variants showed the worst survival curve, followed by not integrated A variants, and finally the non-A variant cases showed no events (P logrank test=0.027).

References

We identified that HPV variant lineages A and DNA viral integration status were related to poor prognosis. This information may help in future clinical management of HPV positive OPC patients. In depth analyses by multivariate approach will be presented at the meeting.

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00409

A p16 oral rinse test to enhance detection of oropharyngeal cancer

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Head and neck cancer remains a challenging disease with the majority of patients diagnosed at an advanced stage when five-year survival is approximately 50%. The main risk factors include tobacco use, excessive alcohol use, betel quid use, and oncogenic HPV virus infection. The incidence of HPV-related oropharyngeal cancer is increasing and differs from traditional oropharyngeal cancer in that it tends to affect younger patients, has distinct biologic characteristics and a better prognosis. In this study we determine whether a surrogate marker for oncogenic HPV cancer, p16, has potential to enhance detection or oral and oropharyngeal cancer when combined with a CD44 and total protein-based point of care (POC) test, used in some countries as an aid in diagnosis.

Results

We selected archived oral rinses that were known to have borderline levels for CD44 and total protein based on results of a prior frequency-matched (for age, race, gender and tobacco and alcohol habits) case: control study. Samples included 19 oral cancer and 17 oropharyngeal cancer patients and 22 controls. We included an additional 2 oropharyngeal cases and 16 normal healthy volunteers that had known borderline CD44 and total protein. We performed a POC test for CD44 and total protein. We used a laboratory test for CD44 and total protein to confirm quantitative results. We then performed a p16 ELISA test on all of the samples to determine whether addition of this test improved POC results. The 22 controls and 16 healthy volunteers were combined to form a larger control group.

Conclusion

Mean CD44 level was 1.33 (range 0.51-2.83) ng/ml for cases and 1.27 (range 0.17-3.52) ng/ml for controls. Mean protein level was 0.38 (range 0.09-0.81) mg/ml for

cases and 0.32 (range 0.01-0.64) mg/ml for controls. Mean p16 level was 148.12 (range 0.00-591.46) ng/ml for cases and 104.31 (range 0.00-686.70) ng/ml for controls. The sensitivity of the CD44 and protein POC test was 23.1% and specificity was 86.8%. When combined with the p16 assay the sensitivity increased to 69.2% and specificity was 50%. The p16 test identified 10 of 13 oropharyngeal cases and 2 of 7 oral cavity cancers that were missed by the POC test. Together the combined p16 and POC tests detected 82% of all oropharyngeal cancer and 100% of the five HPV-related oropharyngeal cancers that were confirmed by p16 pathology.

References

This feasibility study suggests that addition of a p16 assay to a CD44 and total protein POC test may improve sensitivity by 3 times in samples that would likely be missed by the POC test alone. The p16 assay may detect oropharyngeal disease better than oral cavity disease since it is a surrogate marker for HPV. Further study is needed to test these notions.

References

Disclosures: Michael Donovan is a consultant and Chief Medical Officer for Vigilant Biosciences. The University of Miami and Dr. Franzmann hold intellectual property used in the study and have the potential for financial benefit from its future commercialization. Dr. Franzmann is the Chief Scientific Officer, consultant and an equity holder in Vigilant Biosciences, licensee of the IP used in the study.

HEAD AND NECK FORUM

HN6. HPV and non-oropharynx cancers

00548

HPV in Sinonasal Cancers

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

High-risk human papillomavirus (HPV) is well established as a causative agent in oropharyngeal squamous cell carcinoma (SCC). These HPV-related SCC are associated with a significantly improved prognosis. Recently, high-risk HPV has also been recognized as an important driver of a subset of sinonasal tumors. Indeed, the sinonasal tract seems to be a second hotspot for HPV involvement in the head and neck.

Results

This presentation will discuss the role of high-risk HPV in sinonasal tract cancers with a focus on tumor classification and prognosis.

Conclusion

High-risk HPV is responsible for 20-25% of sinonasal SCC. These tumors share the basaloid morphology characteristic of oropharyngeal SCC. Although the prognostic benefit is not as pronounced as in the oropharynx, HPV-related sinonasal SCC also carry a trend toward improved survival. High-risk HPV has also been implicated in non-squamous carcinomas in the sinonasal tract. HPV-related small cell carcinoma is a high grade tumor that can occur in the sinonasal tract and shares the dismal prognosis of conventional small cell carcinomas. In contrast, HPV-related multiphenotypic carcinoma is a recently-described HPV-driven tumor that exclusively occurs in the sinonasal tract and has a uniformly excellent prognosis. Although low-risk HPV has been implicated in a subset of sinonasal papillomas and associated carcinomas, emerging evidence suggests that high-risk HPV does not play a role in these tumors.

References

High-risk HPV has recently emerged as an important causative agent in a broad spectrum of sinonasal tumors, including both SCC and non-squamous tumors.

Although routine HPV testing is not yet recommended in the sinonasal tract, identification of HPV in sinonasal carcinomas can help recognize a distinctive subset of tumors with important prognostic implications.

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00562

Larynx and oral cavity SCC (including P16 as a biomarker for HPV in non-oropharynx cancer)

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papillomavirus (HPV) is an established cause of oropharyngeal squamous cell carcinoma (OPSCC). Of considerable interest is the proportion of non-oropharyngeal head and neck squamous cell carcinomas (NO-HNSCC) that may be attributable to HPV infection and its relationship with patient´s outcomes.

Results

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Conclusion

The HPV DNA prevalence in NO-HNSCC ranged from 0 to 75% in the literature. In a large international study (Castellsagué et al, JNCI 2016), HPV attributable fraction based on HPV-DNA was 7.4% and 5.7% for the oral cavity and the larynx respectively; and it dropped to 3.5% and 1.9% for double positivity for HPV-DNA/p16 ^{INK4a}, highlighting that HPV-DNA is not sufficient to prove viral causation as it might reflect a transient infection. p16^{INK4a} expression is a surrogate marker of HPV involvement and it is the most widely implemented technique in the clinical setting for OPSCC. Nevertheless, research articles have demonstrated that p16^{INK4a} IHC assay alone has very poor positive-predictive-value to diagnosed HPV-related NO-HNSCC (Taberna et al. Oral Oncol 2016). The Guideline from the College of American Pathologist do not recommends routinely HPV testing on patients with NO-HNSCC. Nevertheless, in those cases where the HPV testing is appropriate outside the

oropharynx (i.e. a large tumor comprising an oropharyngeal and a non-oropharyngeal site), HPV-specific testing must be performed beside the $p16^{INK4a}$ assay.

Furthermore, and more importantly for the clinical management, $p16^{INK4a}$ prognostic value in HPV-related NO-HNSCC is controversial. While one study did not find any indication that the prognosis for patients with $p16^{INK4a}$-positive NO-HNSCC differ from patients with $p16^{INK4a}$-negative NO-HNSCC (Lassen et al. Radiotherapy and Oncol 2014) a previous study found that $p16^{INK4a}$-positive NO-HNSCC have significant better outcome compared to the negative group (Chung et al. JCO 2014).

References

HPV testing on patients with NO-HNSCC should not be routinely performed. Nevertheless, in those cases where the HPV testing is appropriate outside the oropharynx, HPV-specific testing must be performed beside the $p16^{INK4a}$ assay.

HEAD AND NECK FORUM

HN7. New perspectives on the clinical care of oropharyngeal cancer

00553

The use of surgery for treatment de-intensification in HPV+ Oropharyngeal Squamous Cell Carcinoma

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Over the last two decades, there has been a rapidly rising proportion of oropharyngeal squamous cell carcinoma (OPSCC) linked to human papillomavirus (HPV). Compared to tobacco-associated, HPV (-) cancers, HPV (+) tumors are generally less aggressive and more likely to respond to new de-intensified treatment regimens. The goal of treatment de-intensification for HPV+ OPSCC is to limit treatment morbidity while maintaining excellent oncologic outcomes. Several methods for treatment de-intensification have been proposed, including through minimally-invasive surgery and through reduction of radiation therapy and chemotherapy dose. In this session, we will discuss the use of surgery in treatment de-intensification for HPV+ OPSCC, with an emphasis on transoral robotic surgery (TORS) and transoral laser microsurgery (TLM). We will discuss the pros and cons of a primary transoral surgical approaches to HPV+ OPSCC, and review current surgical de-intensification protocols.

HEAD AND NECK FORUM

HN8. Risk communication and screening for oral HPV mini-presentations and debate

00599

Incidence of oropharynx cancer and risk groups with oral HPV and Serology to screen

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Will review epidemiology trends of HPV-related oropharyngeal cancer and what the risk groups that are suggested by examining oral HPV and serologic HPV biomarker prevalence.

Results

In session: HN7 Risk communication and screening for oral HPV mini-presentations and debate

HEAD AND NECK FORUM

HN9. Free Communications 3

00241

HEAD AND NECK CANCER WITH “AMBIGUOUS” HPV STATUS: A CASE REPORT

08. HPV testing

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Background / Objectives

According to recent estimates, worldwide 38,000-45,000 cases of head and neck cancer (HNC) are yearly attributable to Human Papilloma Virus (HPV) [1,2]. Patients with HNC HPV-positive tumors have distinct clinical features and a more favorable prognosis compared to HPV-negative HNC [3]. Neoplastic transformation is due to transcriptionally active HPV. For these reasons, it is now crucial to reach a consensus about the combination of tests able to detect transcriptionally active HPV in HNC on archived formalin-fixed, paraffin-embedded (FFPE) tissues. Accurate identification of HPV-driven HNC is a major issue, because the process of fixation and embedding results in a considerable degradation of RNA [4].

Results

Here we report a case of HNC with “ambiguous” results concerning HPV status evaluated by a sequential approach with IHC (with protein P16INK4a Ab) and HPV DNA genotyping (INNO-LiPA Genotyping Extra assay). The in-situ hybridization for E6/E7 mRNA evidenced that our unusual case belongs to the HPV-inactive tumors, in which the virus is a simple passenger, not involved in tumor progression [5].

References

This case underlines the importance of HPV status detection using a method that identify the viral transcription status responsible for oncogenesis [6].

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27. HPV and oropharynx / Head and neck cancer

00010
Enigmatic relation of Human papilloma virus and head and neck cancer

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Oral squamous cell and oropharyngeal cancers (OSCC & OPC) have increased in the past decade especially in the developed countries like UK, USA, Canada, Australia and New Zealand.

The foremost aim of this study was to evaluate the relation amongst the clinical history and histo-pathology of OSCC and OPC patients with Human Papilloma Virus (HPV) infection and to correlate the molecular expression between the HPV positive and negative tumours.

Results

A total of 211 patients were obtained from University College London Hospital (UCLH) data base and information on various clinicopathological parameters. In addition, FFPE samples from 8 tonsillar SCC patients and 16 sites i.e. two sites each from 8 cancer patients (n=8, HPV positive=4×2; HPV negative= 4×2) were micro-dissected, RNA was extracted and expression assay was developed using qRT-PCR. The assay was used to assess various HPV and other genes. The expression assay tested for the following HPV related genes; HPV 16-E6, HPV 16-E7, HPV 18, HPV 33, p16 and exons from two genes implicated in oral cancers; TP53 and PIK3CA.

Conclusion

Statistical significance was found when comparing between progression of disease with medical history (p=0.014), HPV positive tumours and invasion (TNM classification) in the tissues (p=0.014), HPV infected tumours and progression of the

cancer (p=0.037). Analysis of the data from the in house expression assay showed significance when comparing immunohistochemistry HPV positive and negative cases for HPV 16-E6 (p=0.002) and p16 (p=0.009) respectively.

References

The assay's flexibility make it a powerful diagnostic tool for screening multiple patients for virus specific and clinically specific biomarkers for oral cancers. Future study would use this assay to screen a larger cohort of patients with other viral genes and oral cancer related biomarkers.

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00026

Views on, and experiences of discussing HPV with head and neck cancer patients: a qualitative study among health professionals

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Objectives: The prevalence of human papillomavirus (HPV) associated head and neck cancer (HNC) is increasing worldwide. We explored health professionals' experiences of discussing HPV with HNC patients in Ireland.

Results

Interviews (n=20) were conducted with a range of health professionals (including oncologists, psycho-oncologists, ENT surgeons, clinical nurse specialists, speech & language therapists and dentists) involved in the care of HNC patients. Thematic analysis using the Framework Approach was used to analyse verbatim transcripts.

Conclusion

Surgeons and oncologists felt it was beneficial to talk to patients about HPV when initially discussing their cancer diagnosis (particularly in the context of giving patients 'good news'). Others felt there was no point in bringing up the past with their patients. For some, talking about HPV was patient-dependant and often patient-led. Patients rarely initiated HPV discussion. Many HCPs (particularly speech and language therapists and dietiticans) did not see discussing HPV with patients as part of their professional role. Levels of comfort around discussing HPV varied, with some saying they were uncomfortable due to the sexual nature of HPV transmission; others did

not distinguish between talking about HPV and other causal factors like smoking and drinking. Barriers to discussing HPV included: lack of privacy in busy clinics, workload and time constraints, lack of confidence in one's HPV knowledge and worry over possible patient reactions. Many HCPs perceived very low public awareness of HPV and head and neck cancer as inadequate, making it difficult to discuss with patients. While keeping up to date with the latest research on HPV was considered necessary for some, training on how to communicate about HPV (e.g. how to broach the topic) to patients was more important for most HCPs.

References

As far as we are aware, this is the first study of its kind to be conducted in Ireland. HCPs varied in their views and experiences of discussing HPV with HNC patients. The findings may be useful in developing information resources around HPV and head and neck cancer for both patients and health professionals.

00061

Impact of Tobacco Smoking for Patients with Oropharyngeal Squamous Cell Carcinoma and known HPV and p16-status: a multicenter study

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papilloma virus (HPV) and tobacco smoking are important risk factors for development of oropharyngeal squamous cell carcinoma (OPSCC), and highly impacts treatment outcome. The purpose of this study was to evaluate the impact of cumulative tobacco smoking exposurer, in means of numbers of packyears, on overall and progression-free survival for OPSCC patients with known HPV- and p16-status.

Results

Patients diagnosed with OPSCC in Eastern Denmark (2000-2014) and at University Hospital of Giessen, Germany (2000-2009) were included. All tumors were evaluated for p16-overexpression and HPV-DNA. Overall survival (OS) and progression-free survival (PFS) were illustrated with Kaplan-Meier plots. The effect of continuos smoking exposure on survival was evaluated by cox regression models. We defined HPV-positive patients as patient positive for both HPV-DNA and p16.

Conclusion

We included 1316 Danish and German patients diagnosed with OPSCC from 2000-2014 (76% from Denmark), of which 48% were HPV-pos. Smokers had significantly poorer outcome compared to non-smokers, and survival decreased with number of packyears regardless of HPV-status. Considering continuous smoking exposure; Adding 10 packyears of smoking increased hazard ratios irrespective of HPV-status, however this increase was non-significantly greater for HPV-pos. patients (1.05 vs. 1.09).

References

Smoking status at diagnosis significantly impacts survival for patients with OPSCC regardless of HPV-status. There was no significant difference in the effect of cumulative smoking exposure on survival between HPV-pos. and -neg. patients, however there was a tendency towards a greater effect of smoking on survival for HPV-neg. patients at low numbers of packyears, but the disparity to HPV-pos. patients was evened with high numbers of packyears.

00067

Does smoking alter the mutation profile of human papillomavirusedriven head and neck cancers?

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Human papillomavirus (HPV)-driven oropharyngeal cancer (OPC)

patients are characterised by a better prognosis than their HPV-negative counterparts. However,

this significant survival advantage is not homogeneous and among HPV-positive patients

those with a smoking history have a significantly increased risk of oncologic failure. The

reason why tobacco consumption impacts negatively the prognosis is still elusive. Tobacco

might induce additional genetic alterations leading to a more aggressive phenotype. The purpose

of this study was to characterise the mutational profile of HPV-positive OPCs by smoking

status. We hypothesise a higher frequency of mutations affecting smokers.

Results

Targeted next-generation sequencing of 39 genes that are recurrently mutated in

head and neck cancers (HNCs) caused by tobacco/alcohol consumption was performed in

62 HPV-driven OPC cases including smokers and non-smokers.

Conclusion

The study population included 37 (60%) non-smokers and 25 (40%) smokers. Twenty

(32%) patients had no mutation, 14 (23%) had 1 mutation and 28 (45%) had 2 or more mutations.

The most commonly mutated genes regardless of tobacco consumption were PIK3CA

(19%), MLL2 (19%), TP53 (8%), FAT 1 (15%), FBXW7 (16%), NOTCH1 (10%) and FGFR3

(10%). Mutation rate was not significantly different in smokers compared with non-smokers

even when analyses focused on heavy smokers (>20 pack-years vs. <20 pack-years). Similarly,

there was no significant difference in mutations patterns according to tobacco consumption.

References

In HPV-positive patients, smoking does not increase the mutation rate of genes

that are recurrently mutated in traditional HNC. Additional studies are warranted to further

describe the molecular landscape of HPV-driven OPC according to tobacco consumption.

00093

Association between oropharyngeal cancers with known HPV and p16 status and cervical intraepithelial neoplasia: A Danish population-based study

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Persistent infection with high-risk genotypes of human papillomavirus (HPV) is the main risk factor in the development of uterine cervical precancerous lesions and cervical cancer (CC). Furthermore cases of HPV-induced oropharyngeal squamous cell carcinoma (OPSCC) is increasing in the Western world. We investigated the association between HPV and p16 status and previous results of cervical examinations, including cytological and histological tests, in females with OPSCC.

Results

We included females diagnosed with an OPSCC in Eastern Denmark from 2000-2014. Tumours were assessed for p16-overexpression and HPV DNA PCR. History of cervical tests was obtained from the Danish Pathology Registry. The cytology and histological results were categorized in accordance with the 2014 Bethesda System (TBS) and WHO. Hence, we divide the cervical results into two groups. Group I were negative for intraepithelial lesion or malignancy and group II had epithelial cell abnormalities and subdivided after increasingly neoplastic severity from A-D. Chi^2-tests and Fischer's exact tests were performed to compare the two groups.

Conclusion

A total of 417 women with OPSCC were identified; 203 with HPV-positive tumours (49%) of which cervical cytology or histology were available in 172 women (85%). Among these, 22 (13%) patients had a cervical history of ≥ IIC. A total of 171 out of 214 women in the HPV-negative group (80%) were examined with cytology and 17 had a history of ≥ IIC. No significant difference in diagnoses of (pre)cancerous lesions between the OPSCC HPV-positive and negative groups were observed (χ^2 test $p = 0.28$, Fischer's exact test $p = 0.29$).

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HPV status in oropharyngeal tumours was not correlated with a history of ≥ IIC in cervical examinations but interestingly a possible effect on cervical dysplasia may be masked by a higher incidence of smoking among the OPSCC HPV-negative group.

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00096

COMORBIDITY IN HPV+ AND HPV- OROPHARYNGEAL CANCER PATIENTS: A POPULATION-BASED, CASE-CONTROL STUDY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Comorbid conditions severely impact outcome for patients treated for oropharyngeal squamous cell carcinoma (OPSCC). Comorbidities serve as competing risk factors for death and may affect the ability to complete therapy and adhere to follow-ups. The purpose of this study was to investigate comorbidities in patients with OPSCC and known HPV-DNA.

Results

We included patients diagnosed with an OPSCC in Eastern Denmark in 2000-2014. Patients were linked to the Danish National Patient Register to identify comorbidities based on the Charlson Comorbidity Index (CCI) at time of diagnosis and following cancer treatment. Patients were age-and sex-matched in a 1:10 ratio with a reference group and stratified according to HPV-status.

Conclusion

In total 1,499 patients (55.0% HPV+) and 14,990 controls were included. Significantly more HPV+ patients did not have comorbidities compared to HPV- patients both at the time of diagnosis (RR: 1.5 (1.3;1.6)) and following cancer treatment (RR 1.5 (1.4;1.6)). Most prevalent comorbidity was malignancy not including the OPSCCs (n=582) accounting for both HPV+ and HPV- patients. HPV+ patients had an increased risk of AIDS (OR: 4.2 (1.6;11.0)) compared to the reference population. HPV- patients had increased risk of cerebrovascular disease (OR: 1.4 (1.1;1.8)), peripheral vascular disease (OR: 1.7 (1.3;2.3)), ulcer disease (OR: 2.5 (1.9;3.2)), and liver disease, both mild (OR: 6.7 (5.1;8.9)) and severe (OR: 7.6 (5.1;11.3)).

References

This population-based study showed that HPV- patients had more comorbidities than HPV+ patients at the time of OPSCC diagnosis and in regards to comorbidities acquired after the cancer diagnosis. OPSCC patients had a significant increased risk of malignancy compared to the reference population with most frequent location being oral cavity cancer.

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00353

PLASMA HPV CELL-FREE DNA AND HPV-RELATED HNSCC

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Recently, digital PCR, a highly sensitive PCR system, has been introduced into various clinical diagnoses. Among them, liquid biopsy targeting blood circulating tumor-derived DNA is expected as a system that enables early cancer detection its monitoring by a minimally invasive and simple method. However, in human papilloma virus (HPV) positive head and neck squamous cell carcinoma (HNSCC), the effectiveness of liquid biopsy has not been fully evaluated yet. In this study, we used digital PCR to quantify circulating HPV-DNA copy number in plasma and examined its clinical relationship.

Results

We enrolled 24 patients with HPV type 16 DNA positive and p16 IHC positive HNSCC from August 2017 to July 2018. These clinical stages were classified by using UICC 7th edition. DNA was extracted from 3 ml of plasma using QIAamp Circulating Nucleic Acid Kit (QIAGEN) and the virus copy number per 1 ml of plasma was quantified by digital PCR (Bio-Rad QX200). We quantify the HPV DNA existance using primer sets for both HPV type 16 DNA early lesion (E6, E7).

Conclusion

Plasma HPV-DNA can be detected in all cases except for 2 cases of early lesion using digital PCR (median; 1133.5, range; 0-333333 copy number / ml). Plasma HPV-DNA copy number was correlated with N, M classification rather than T classification. Plasma HPV-DNA can be detected in 4 of 5 patients with residual tumor, and not detected in 10 of 11 cases that was evaluated as complete response using PET-CT. In only one case of them, its PET-CT showed positive uptake, but HPV-DNA in plasma did not existed. Thus, we performed biopsy in this region, that is diagnosed as no malignancy. Furthermore, we analyze the correlation between HPV-DNA amount and various clinical parameters.

References

Circulating HPV DNA was associated with disease extent and treantment response among patients with HPV-related HNSCC.

00495

HPV PREVALENCE AND OVERALL SURVIVAL IN A COHORT OF PATIENTS WITH TONSILLAR CANCER TREATED WITH RADIATION THERAPY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

During the last decades, the prevalence of oropharyngeal cancer (OPC) has increased in many countries. The link between persistent infections with human papilloma virus (HPV) and OPC is well established. The increased incidence is assigned to the HPV-positive cases.

The treatment for OPC is most often chemoradiotherapy (CRT) and/or surgery but clinical trials are investigating the possibility to a milder treatment using only radiotherapy (RT) or surgery.

Örebro county is located in central Sweden and has around 300 000 inhabitants. The largest city has 150 000 inhabitants. At Örebro University Hospital, a tertiary referral hospital, we have treated around 600 patients from Örebro and other counties with tonsillar cancer (TC) between the years 1988-2014 primarily with RT alone. In very advanced cases, CT could be added, while surgery was used only as salvage, mainly in the neck. In many centers in Sweden the standard of care has been to treat only the more advanced cases of stage III-IV oropharyngeal cancer with chemoradiotherapy. Analyses of treatment results has shown results with RT alone quite comparable to those with CRT.

Results

The cohort consists of 98 patients presented consecutively from Örebro county itself with TC during the years 1988-2014, diagnosed and treated at Örebro University Hospital. HPV status in the tumors was retrospectively assessed in formalin fixed paraffin embedded tissue using Anyplex 28 (Seegene), detecting 28 different HPV genotypes.

Conclusion

Of the 98 patients, 72 (73%) were HPV positive. HPV 16 was the absolute dominating genotype, detected in 67/72 cases. HPV 33 and 35 were seen in 2 cases each and HPV 31 in one.

The tumor status (T) was comparable between the HPV positive and negative groups, while the nodal status (N) was more advanced in the HPV-positive group. Two patients declined treatment and one had had previous irradiation in the area. All others were given RT (95/98). CT was given to 8% of the HPV negative patients and 21% of the positive group. About ¼ patients in both group required salvage surgery of the neck. The overall 5-year survival was similar in the two groups (HPV negative 73%, HPV positive 71%), while a smaller percentage of patients in the negative group died with an active tumor (12 compared to 21 %)

References

This retrospective study finds that RT as a primary treatment seems to be effective. Surprisingly HPV status of the tumor had no major impact on overall survival after RT in our study. However, it seems that HPV-positive tumors presented at a more advanced nodal stage.

00505

THE FRACTION AND NUMBER OF HEAD AND NECK CANCERS ATTRIBUTABLE TO HPV IN CANADA

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

The presence of human papillomavirus (HPV) in cancer tissue can indicate its involvement in cancer. The detection of E6 and/or E7 oncoproteins has emerged as the gold standard for attributing head and neck cancers (HNCs) to HPV, yet in practice other techniques are frequently used to assess HPV status in HNCs. On behalf of the ComPARe Study Group, we estimated the fraction and number of HNCs in Canada attributable to HPV detected via different methods.

Results

We searched the literature and reviews for studies reporting on HPV prevalence in primary tumours of the oropharynx, oral cavity, or larynx diagnosed among patients in Canada or the United States. Data were pooled assuming random effects and 95% confidence intervals (CIs) were calculated. Study heterogeneity was assessed with the index of consistency. The number of attributable cases was calculated by multiplying the attributable fraction by the number of relevant cancers diagnosed in 2015 among Canadians aged 18 and older. Cancer incidence data were obtained from the Canadian Cancer Registry governed by Statistics Canada.

Conclusion

We included 37 studies in the analysis. Estimates of the attributable fraction of HPV in cancers of the oral cavity ranged from 5% to 11%, in oropharyngeal cancers from 54% to 69%, and in laryngeal cancers from 8% to 19%. Among Canadians aged 18 and older in 2015, there were 1,480 HPV-attributable HNCs based on HPV DNA

detection via PCR, 1,330 based on HPV-16 PCR, 1,095 based on HPV-16 E6/7, and 1,455 based on p16 detection. Heterogeneity was significant for all cancer sites and detection methods.

References

HPV-16 E6/7 produced lower but not significantly different HPV prevalence estimates compared to the other detection methods. Our estimates suggest that 1,095 (95% CI: 790−1,481) HNCs diagnosed in 2015 could have potentially been prevented if HPV were eliminated in Canada. This analysis reveals the considerable potential for the prevention of HNCs attributable to HPV-16.

HPV prevalence in head and neck tumour sites by different detection methods in North American populations

Tumour site	HPV detection methods			
	HPV DNA via PCR % (95% CI)	HPV-16 via PCR % (95% CI)	HPV-16 via E6/7 % (95% CI)	p16 % (95%CI)
Oral cavity	11 (8–15)	9 (5–13)	5 (1–10)	11 (5–20)
Oropharynx	64 (53–73)	57 (45–70)	54 (45–63)	69 (60–77)
Larynx	19 (11–28)	19 (10–29)	8 (0–22)	9 (1–24)

EUROGIN 2018 Abstracts

PART II - FREE COMMUNICATION SESSIONS

FC 01. Screening 1

00552

Molecular characterization of HPV16 sub-lineages: viral sequences, integration events, and human somatic mutation landscape

01. Viral and molecular biology

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Background / Objectives

Cervical cancer is the most frequent cause of cancer mortality for women living in poverty and is almost exclusively caused by the human papillomavirus (HPV). To better understand the molecular characteristics of HPV and the cervical tumor genome we have surveyed 665 cases of cervical cancer from Guatemala.

Results

Tumor DNA was sequenced by the capture of the exons of 245cancer-related genes, and variants called, and somatic mutation filtered. HPV 16 DNA was sequenced using a previously validated panel of overlapping primers, aligned to the viral genome and sub-lineage determined by phylogenetic analysis.

Conclusion

The average age is 52 and the number of children is 6.0, 5.6% report tobacco use; 56% have stage 2 or 3 cancer and 82% of tumors are squamous cell carcinoma. In total, 20% of subjects report a family history of any cancer and 6% for cervical cancer. Patients with a family history of cervical cancer have a younger age of onset

(47 years) and were pre-menopausal cancer (57% versus 42% in the entire sample). In total, 11/24 tumors have a mutation in the *PIK3CA* gene (46%) and 58% of tumors have at least one mutation in the PI3K pathway. Other known driver mutations include *TP53*, *RB1*, and *CASP8*. Mutations in chromatin remodeling genes (*PBRM1*, *EP300*, *SMARCA4*, *KMT2C*, *KMT2D*, *HIST1H3B*, *HIST1H4E*, *HIST1H1E*) are also elevated with 46% of tumors having at least one mutation. Tumors have an average of 18 mutations (median 14); however, 4 tumors have high (32-38 mutations) or very high (63-64) mutation load. All hypermutation subjects have *PIK3CA* mutations and are post-menopausal. Mutation signature analysis shows that the highest signature is for APOBEC-related mutations (46%) and HPV is known to activate APOBEC. Pre-menopausal patients have a lower mutation load (mean 13 mutations) and a lower fraction of APOBEC-related mutations (40%). Overall HPV16 accounts for 58% of HPV infections in Guatemala. We have sequenced and variant classified 96 HPV16+ cervical cancers and found that the D2 and D3 sub-lineages represented 26% and 29% of the samples, respectively. A total of 65% (62/96) of the samples had integrated HPV16 sequences as determined by HPV DNA capture and sequencing, and A1 and D2 sub-lineages showed a higher frequency of integration 78-79%) compared to D3 (44%). Subjects with HPV16 integration have a significantly younger age (P=0.009), and D2 was observed in younger patients, as compared to A1 (P=0.001).

References

Guatemalan cervical tumors have a similar profile of somatic mutations to those in the US, with a high frequency of *PIK3CA* mutations, and the very high-risk HPV16 D2, D3 sub-lineages.

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00556

3D Squamous Epithelial Tissue Culture System for Anti-HPV Drug Discovery and Validation

01. Viral and molecular biology

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Background / Objectives

Management of HPV lesions requires better therapeutic options than are presently available. We established a three-dimensional epithelial tissue culture system from primary human keratinocytes harboring HPV-18 replicons, fully recapitulating a robust infectious program (Wang et al. 2009). Systematic investigations of virus-host cell interactions in such 'raft' cultures grown at the liquid medium/air interface (Dollard et al. 1992; Wilson et al. 1992) have identified critical regulatory pathways on which HPV DNA amplification depends, revealing potential host targets for anti-viral therapies. Our strategy is to repurpose existing pharmacologic agents to inhibit viral DNA amplification, interrupt HPV transmission, or preferentially eradicate HPV-infected cells.

Results

Inhibitors are delivered to HPV-18 infected as well as to uninfected control PHK raft cultures either topically or through the tissue culture medium for up to two weeks before harvesting the tissues. In addition, durability of responses is evaluated after a post- exposure chase period. We then probe FFPE tissue sections for HPV DNA amplification, cellular DNA replication, papillomaviral proteins E6, E7 and L1, targeted host proteins, and tissue morphology, as well as for markers of DNA damage and apoptosis. Duplicate rafts are used for HPV DNA copy number evaluation to ascertain that there is a wide dynamic range between unimpeded viral DNA amplification and inhibited infections, typically 100-fold or more. Additional cultures can be used to evaluate specific mRNAs and micro-RNAs. Rafts can also be established from HPV-immortalized or -transformed epithelial cells or cervical cancer cell lines. Moreover, 3D cultures can be grown directly from patient lesions.

Conclusion

Based upon host cell metabolic and regulatory pathways essential for maintenance of the viral genome, replicative amplification and virion morphogenesis, we are systematically investigating inhibitors of mitogen-activated protein kinases, histone deacetylases, DNA Damage Responses including cell cycle checkpoints (Banerjee et al, 2011), replicative DNA amplification, and cytoplasmic vesicle function as well as inducers of stress responses. Using the 3D raft culture system, we have identified molecularly distinct inhibitor candidates as safe and effective. Several such agents are advancing to clinical trials to treat benign HPV lesions (Banerjee et al., 2018).

References

These proof-of-principle experiments demonstrate the potential for discovery of new drugs against epitheliotropic viruses. The authenticity of 3D experimental models of HPV infections and diseases should greatly reduce preclinical research time and expense.

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00630

Is HPV-negative cervical cancer a biologically different entity?

02. Epidemiology and natural history

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Background / Objectives

High risk human papillomavirus (hrHPV) infection is established as the major cause of invasive cervical cancer (ICC). Yet there seems to be a subset of cervical cancers where hrHPV is not readily detectable in the tumor tissue by standard PCR methods.

Methods

We recently described findings from an analysis of national registers and comprehensive HPV genotyping of all cervical cancer cases diagnosed in Sweden during the years 2002-2011.

Results

Of the 2845 included cases, hrHPV was detected in 2293 cases (80.6%) using general primer PCR with Luminex genotyping and real-time PCR targeting the E6/E7 regions of HPV16/18. Women with hrHPV-positive cervical tumors had a substantially better prognosis than women with hrHPV-negative tumors, independently of already established clinically relevant factors.

Conclusion

This raises the question whether L1 negative tumors are biologically different from L1 positive tumors. In this presentation, we will discuss different definitions of hrHPV

negativity, sensitivity of laboratory detection methods, and resulting implications for research and practice.

00057

Screening of cervical cancer in women aged 30 to 64 years screened with human papillomavirus tests (ESTAMPA* study). Experience in Paraguay.

09. HPV screening

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Background / Objectives

Paraguay has high incidence and mortality rates of cervical cancer of 34,2 y 15,7 x 100.000 women respectively.

The objective of this cross-sectional study was to assess the feasibility of implementing organized cervical cancer screening programs based on high risk human papilomavirus (HR-HPV) testing within the health system of Paraguay.

Results

The invitations to carry out the screening were made with house-to-house visits in communities of Itaugua and San Lorenzo, to women between 30 to 64 years old, period 2014-2017. All eligible women were invited to nearest health centers and institutions that had a room enabled to perform cervical samples collection to be screening by HPV test. Cervical samples were collected in PreservCyt medium and HR-HPV were deteted by Hybrid Capture 2. HR-HPV positive women were referred to colposcopy and, biopsies were taken in cases of abnormal colposcopic impressions. All the women with an anatomopathological diagnosis of cervical intraepithelial neoplasia (CIN2 +) were directed to treatment and all HR-HPV women with CIN 1 or less are being invited to a control visit at 18 months with the HPV test. The ESTAMPA study group received previous training to conduct home visits, sample collection, sample processing, colposcopic and anatomopathological evaluation. An internal and external quality control system were established.

Conclusion

A total of 5321 women were enrolled in the study, corresponding an average of 59% of elegible women invited to carry out the screening with a minimum participation of 44% and a maximum of 78% per community included. The prevalence of HR-HPV was 14%. Ninety percent of women attended the colposcopy visit and 1.3% were CIN2 +. Seventy-nine percent were treated by the ESTAMPA study group gynaecologists and the rest of CIN2+ women reported receiving treatment at other health centers.

References

It was possible to carry out an organized screening model achieving, an average of 59% participation in screening, 90% compliance with colposcopy among HR-HPV positive women and identifying a high prevalence of 1.3% of CIN2+. The ESTAMPA study group was able to treat 79% of cases. These results suggest the importance of strengthening screening and follow-up of women at risk of developing cervical lesions through organized programs based on sensitive molecular tests.

References

* ESTAMPA study: a multicenter study of screening and triage of cervical cancer with human papillomavirus tests.

00080

HPV- DNA primary screening in Israel decreased colposcopy referrals – The experience of Maccabi Health Medical Organization

09. HPV screening

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Background / Objectives

The primary cytological screening for detecting cervical cancer and precancerous lesions (PAP-smear) has been proven in reducing morbidity and mortality of cervical cancer when performed once every 3 years. The main disadvantage of cytology is its low sensitivity. In order to improve the sensitivity of the survey to detect malignant and pre-malignant lesions it has been proposed to use HPV-DNA primary screening instead. Maccabi HMO (220000 affiliates, 25% of the Israeli population) started to use HPV-DNA primary screening based on HPV DNA only test (cobas test , roche) at 1/3/18, with triage of cytology and genotyping for the referral to colposcopy.

Objective: To compare the rate of referral to colposcopy based on two primary screening methods (HPV vs PAP tests) in the Israeli population.

Results

Data was collected for each screening-group based on a centralized computerized system. The sreening was done for women aged 25-65 in both groups. The time periods were 1.1.2017 to 31.12.2017 for the cytology screening, and 1.3.2018 to 21.5.2018 for the HPV-DNA screening. In the primary-cytology era, women with abnormal cytology (>LGSIL) or accasionaly with ASCUS, were referred for colposcopy. During the primary HPV-DNA screening, women that are found positive for HPV 16/18 or positive for other High-Risk HPV with abnormal cytology were referred for colposcopy. We are comparing the rate of referral for colposcopy during the two methods of primary screening

Conclusion

21,033 women with primary-HPV-screening tests during the study period, were compared to 112000 women screened by primary-cytology. In the primary HPV-DNA screening group 726 women (3.45%) were referred for colposcopy, of which 2% were positive for HPV 16-18 and 1.45% positive for other HR-HPV with abnormal cytology. In the primary cytology screening era 7392 women (6.6%) were referred for colposcopy of which 4.1% had abnormal cytology > LGSIL and the rest (2.5%) from the ASCUS group. The differences were found to be statisticalyl significant by chi-square analysis (OR=0.51, 95% Confidence Interval, 0.46-0.56, p-value < .00001) favoring primary-HPV screening

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Primary HPV-DNA screening in Israel decreases significantly the rate of referral for colposcopy, when compared to primary-cytology screening.

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00101

IMPLEMENTATION OF PRIMARY HPV mRNA SCREENING FOR CERVICAL CANCER: FIRST YEAR EXPERIENCES

09. HPV screening

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Background / Objectives

Primary HPV screening for cervical cancer by HPV mRNA testing (APTIMA) was implemented in January 2017, for women ≥30 through 70 years in the region of Skåne, Sweden. HPV positive samples underwent cytology triage, and women with abnormal cytology for atypical squamous cells of undetermined significance + (ASCUS+) were referred to colposcopy. The aim was to perform an audit of the primary HPV screening program year 2017, and to compare its cytology results to that of corresponding women aged ≥30 through 65 years screened with cytology during 2016.

Results

The present audit was register-based. The Aptima HPV assay (Hologic) was performed according to the manufacturer's instructions using the Panther platform (Hologic). Primary HPV screening starts at >30 years. Women not attending the final invitation at 65 years receive re-invitations up 70 years. During 2017 62,971 women were analysed for presence of HPV within the primary HPV screening. In order to ensure that the primary HPV screening program also detects the few cases of cellular changes that may occur without an active HPV infection 5,027 women aged 40-42 years were co-tested. We compared proportions of abnormal cytology between cytology screening and primary HPV screening of women aged 30-65 years. Data from cytology screening (N=45,754) were collected from 2016, and from primary HPV screening during 2017 (N=49,774). The cytology screened and the primary HPV screened women had the similar age distribution (Table 1).

Table 1.Proportion of women stratified by age.

AGE	2016 Cytology#	2016 Cytology Proportion %	2017 HPV#	2017 HPV Proportion%
30-39	16664	36.4	17287	34.7
40-49	16132	35.3	16075	32.3
50-65	12968	28.3	16412	33.0
Total#	45764	100	49774	100

Conclusion

HPV was detected among 7.0% (4,422/62,976) of the women 2017. Among a control group of the screening population with co-testing (cytology and HPV) aged 40-42 years (N=5,027), HPV was detected in 100% (28/28) of high-grade squamous intraepithelial lesion (HSIL) and among ASCUS where HSIL could not be excluded (ASC-H) (9/9), and 80% (4/5) of atypical glandular cells (AGC). Thus, within this group the sensitivity of the HPV mRNA test to detect severe dysplasia was 98% (95% CI; 87% to >99.9%).

The proportion ASCUS+ was 3.38% and 3.70% with cytology and primary HPV screening, respectively (P=0.0080). Only the proportion of ASC-H cytology changed by the use of primary HPV screening, from 0.13% to 0.23% (p<0.001).

References

Primary HPV mRNA screening for cervical cancer screening marginally increased (0.32%) the proportion of women with ASCUS+ cytology.

Cytology decreased by 83% within our primary HPV screening of women aged 30 through 70 years, due to the relatively low amount of cytology triaged samples and the co-testing cytology performed.

00113

RISK OF CIN2+ AFTER A NEGATIVE 1-YR RECALL HPV TEST IN HPV-POSITIVE WOMEN WITH NORMAL CYTOLOGY ATTENDING HPV CERVICAL SCREENING

09. HPV screening

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Background / Objectives

In Italy, women screened by HPV testing undergo cytology triage in case of positivity; those with normal cytology repeat HPV testing after 1 year, and return to routine screening in case of negativity. We evaluated their subsequent CIN2+ risk in order to define a safe screening interval.

Results

We analyzed the data from four Italian pilot projects (Alta padovana, Monselice, Padova and Vallecamonica) that nested HPV screening implementation within organized cervical cancer screening programs, enrolling 25-64 yrs-old women presenting for a new screening round. Search for high-risk HPV (hrHPV) DNA was performed by Hybrid Capture 2 (HC2, Qiagen). According to the protocol, both HPV-negative women and HPV-positives testing negative at 1-yr repeat returned to screening after three years. We compared HPV test positivity, CIN2+ and CIN3+ detection at 3-year re-screening in the 688 women with such transient infections to those in the 53,405 women HPV-negative at the previous screen.

Conclusion

At the second screening round, among women with previous transient infection, 105 tested HPV-positive and 6 CIN2 and 2 CIN3, but no cervical cancer, were detected. Compared with previously HPV-negative women, HPV infection among women transiently HPV-positive was four times more frequent (15.3‰ vs 3.9%, respectively. Relative Risk 3.93; 95%CI 3.15-4.85). The detection of CIN2 was fourteen times

more frequent (8.7‰ vs 0.6‰, respectively. RR 13.7; 95%CI 4.7-33.1) and the detection of CIN3 eight times more frequent (2.9‰ vs 0.4‰, respectively. RR 7.8; 95%CI 0.9-32.0).

References

Women with hrHPV infection without cytological abnormalities and undetectable HPV at short-term repeat have higher rates of HPV infection and of detection of CIN2 and CIN3 lesions at the subsequent screening round. According to European and Italian guidelines, these women return to regular screening, and some concern has been raised on the safety of a five-year interval. At a 3-year re-screening, we observed higher rates mainly of CIN2 lesions. The detection of CIN3 is similar to that observed in routine European cytology-based screening programs (2.7‰), showing that this level of risk is considered as acceptable. The evaluation of results from other pilot projects is planned.

00230

SAFETY AND EFFICACY OF PROPHYLACTIC HPV VACCINES. A COCHRANE REVIEW OF RANDOMISED TRIALS

09. HPV screening

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Background / Objectives

Recently, the evidence on efficacy and safety of prophylactic HPV vaccines derived from randomised controlled trials (RCTs) was published in the Cochrane database of Systematic reviews. A summary of this Cochrane review is presented below.

Results

Only RCTs involving mono-, bi- and quadri-valent HPV vaccines were included. Trials evaluating the nona-valent vaccine were excluded since women in the control group received the quadri-valent vaccine. Main outcomes were: histologically confirmed cervical precancer lesions distinguishing those associated with vaccine HPV types and any cervical precancer. Exposure groups were: young women (15-26 years) or mid-adult women (24-45 years) being initially negative for high-risk HPV (hrHPV) or negative for HPV types included in the vaccine and women unselected by HPV status.

Conclusion

All evaluated vaccines offered excellent protection against cervical intra-epithelial neoplasia of grade 2 or 3 (CIN2/CIN3) and adenocarcinoma-in-situ (AIS) associated with HPV16/18 infection in young women who were not initially infected with hrHPV or HPV16/18. Vaccine efficacy decreased when women regardless of HPV DNA status at enrolment were included. Vaccine protected also in young women but at a lesser degree against any cervical precancer. Vaccine efficacy was lower in mid-adult women. Trials were not empowered to address protection against cervical cancer. Occurrence of severe adverse events or adverse pregnancy outcomes was not significantly higher in recipients of HPV vaccines than in women included in the control arms.

References

To complete evidence from randomised trials, careful population-wide surveillance of HPV vaccine effectiveness (targeting also incidence of HPV-related cancers) and safety (including also rare conditions such as neurologic and auto-immune syndromes) should be set up by linking vaccination, cervical cancer screening and morbidity registries.

References

KEYWORDS: Cervical cancer, HPV vaccines, safety, randomised clinical trials, systematic review, meta-analysis.

00317

Accuracy of high-risk HPV testing and HPV16/18 genotyping to triage women with LSIL: a pooled analysis of VALGENT studies

09. HPV screening

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Background / Objectives

Genotyping for the most carcinogenic HPV types (HPV16 and HPV18) could identify those women at highest risk requiring colposcopy or more intensive follow-up in women with low-grade squamous lesions (LSIL).

Results

The VALGENT framework is designed to assess the analytical and clinical performance of HPV tests that offer limited to extended genotyping capability. VALGENT is iterative using panels collated in different countries. A pooled analysis was performed, using data from three completed VALGENT panels, to assess the diagnostic accuracy of genotyping for HPV16/18 and for hrHPV (13 or 14 types) to detect prevalent CIN2+ in women with LSIL. Data pooling was performed using a bivariate normal model designed for meta-analysis of diagnostic test accuracy, taking the intrinsic negative correlation between sensitivity and specificity into account.

Conclusion

Twenty HPV tests were evaluated within three VALGENT panels. The pooled sensitivity and specificity of hrHPV in aggregate to detect CIN2+ was 98.1% (95%CI: 95.5 -99.2%) and 23.8% (95%CI: 20.6-27.3%) in women with LSIL, respectively. HPV16/18 genotyping had a sensitivity and specificity for CIN2+ of 56.2% (CI: 51.0-61.3%) and 77.1% (CI: 73.0-80.8%), respectively. HPV16/18 genotyping was substantially more specific (ratio: 2.65, 95%CI: 2.13-3.28) but also less sensitive than testing for hrHPV (ratio: 0.62, 95%CI:0.57-0.68). No significant inter-panel

differences were observed either for the pooled analysis of hrHPV test accuracy or theHPV16/18 genotyping. The average risk of underlying CIN2+ was 39.7% in HPV16/18-positive women with LSIL, 13.1% in women who were HPV16/18-negative but positive for other hrHPV types and 2.1% for hrHPV-negative women.

References

Triage of women with LSIL with partial genotyping identifying HPV16/18 increases the PPV compared to hrHPV but at the expense of lower NPV. Women testing positive for HPV16/18 need further diagnostic and/or therapeutic work-up. Women testing HPV16/18-negative but positive for other types may also be referred to colposcopy whereas hrHPV-negative LSIL patients also should be kept under surveillance. Further development and optimization of triage markers are needed to manage women with LSIL.

00320

mRNA HPV E6/E7 SCREENING: A 3-YEAR LONGITUDINAL COTEST STUDY IN MADRID. PRELIMINARY RESULTS.

09. HPV screening

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Background / Objectives

There are few studies measuring the risk of a high-grade (CIN2+) lesión after a negative Aptima®high-risk mRNA HPV test (AHPV) (1-3). In the first published pilot study in Madrid, a baseline screening cotest with cytology and AHPV on 5.053 women aged 25-65, yielded a 9% AHPV prevalence and a 26,3% rate of CIN2+ lesions in AHPV-positive biopsied women (4).

The objective of the present study is to analyze the negative predictive value (NPV) of the mRNA HPV test with a longitudinal analysis at 3-years of the previously screened population.

Results

So far, 520 women with a baseline AHPV-negative result have been actively recruited by phone call for a new cotest analysis 3 years later. Cervicovaginal samples were obtained from a health care professional and placed into ThinPrep® PreservCyt solution. Simultaneous cytology with a ThinPrep® 5000 processor and AHPV analysis with the automated Panther® platform was performed. AHPV-positive women or those with LSIL+ cytology results were referred to colposcopy and biopsy or endocervical curettage.

Conclusion

The prevalence of AHPV in this longitudinal phase was 3,8% (20/520) and the age was significantly lower in AHPV-positive than in HPV-negative women (41,4 vs 46,15 years, p=0,017). There was a histological analysis in 65% of AHPV-positive women (13/20), yielding 4 CIN1 and 1 CIN3 lesions. From these, only the woman with a

CIN3 had abnormal cytology (HSIL). From the 500 AHPV-negative women, there were 3 cases with cytological ASCUS and 1 with an LSIL diagnosis (0,8%).

References

The prevalence of AHPV decreased from 9% in the baseline study to 3,8% three years after a negative AHPV test. Infected women were significatly younger than those AHPV-negative ones, suggesting new infections. The risk of harboring a CIN2+ lesion in the AHPV-positive group of the longitudinal study was 7,7% as compared to 26,3% of the baseline. Therefore, preliminary results of this study demonstrate a low risk of a high-grade cervical lesion 3 years after a negative AHPV test.

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00363

CERVIVA HPV Primary Screening Pilot Study: evaluation of triage strategies for HPV-positive women

09. HPV screening

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Background / Objectives

Triage of HPV positive women is one of the key challenges facing HPV primary screening. Specific second round triage tests to avoid large numbers of unnecessary referrals to colposcopy are required. This study investigates a panel of triage options including HPV16/18 genotyping, cytology and dual staining for p16/Ki-67 in women who test positive for HPV in primary screening.

Results

In partnership with CervicalCheck, The National Cervical Screening programme, CERVIVA are undertaking a longitudinal observational HPV primary screening study which will evaluate different triage strategies for management of a HPV-positive primary screening test. Cervical cytology samples from approximately 13,000 women undergoing routine cervical screening were tested for HPV DNA (cobas 4800 HPV test) and mRNA (Aptima HPV assay). All HPV-positive women were further assessed with HPV16/18 genotyping, cytology and p16/Ki-67 dual staining. The performance of different triage strategies was examined both cross-sectionally and will be longitudinally assessed over two screening rounds for detection of CIN2+.

Conclusion

12,608 eligible woman have been recruited into the study. The median age of the population is 38 years. HPV DNA testing, performed on 10,528 samples, shows a 15.7% positivity rate. HPV mRNA, performed on 12,601 samples, gave a 12.8% positive rate. Overall, 31.2% (514/1650) of HPV DNA positive women were positive for HPV16/18, 33.2% (548/1650) had an abnormality on cytology and 32.8% (274/836) tested positive for p16/Ki-67. p16/Ki-67 demonstrated the highest sensitivity and specificity for detection of CIN2+ (0.91, 0.78 respectively), when combined with HPV16/18 genotyping sensitivity was similar but specificity was significantly reduced (0.93, 0.67 respectively).

References

Here we present the preliminary cross-sectional data in relation in to each of the putative triage tests. p16/Ki-67 appears to be a sensitive and specific triage test for women who test positive for HPV in primary screening.

00396

ABSOLUTE AND RELATIVE RISK OF CIN2/3+ IN WOMEN ASCUS HPV16/18+ VERSUS ASCUS 12OTHER HRHPV+: BASELINE RESULTS OF THE COMPACT STUDY−

09. HPV screening

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Background / Objectives

While cytology-based screening programs have significantly reduced mortality and morbidity from cervical cancer, the global consensus is that primary human papillomavirus (HPV) testing for cervical screening increases detection of high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer. However, the optimal triage strategy for HPV positive women to avoid over-referral to colposcopy may be setting specific. As Japan requires data generated domestically to modify screening guidelines, we conducted a 3-year prospective study, COMparison of HPV genotyping And Cytology Triage (COMPACT), to evaluate the potential role of HPV16/18 partial genotyping and cytology for primary HPV screening. This study compares absolute and relative risk of ≥CIN2/3 at baseline in women ASCUS HPV16/18+ compared to those ASCUS 12other hrHPV+.

Results

Participants were 14,642 women aged 20-69yrs attending for screening at Hokkaido Cancer Society in 3 cities in Hokkaido, Japan, between April 2013 and March 2014. Women with ASCUS or worse cytology, regardless of HPV status, and NILM HPV16/18+ went straight to colposcopy. Women NILM 12other hrHPV+ underwent repeat cytology after 6m and those with ≥ASCUS went to colposcopy. The present analysis focuses on 14,500 women aged 25-69yrs.

Conclusion

Totally, 150 (1.03%) women had ASCUS cytology. Mean age was 44.4 yrs. Overall, 86 cases were hrHPV- and 64 hrHPV+. In the latter, 19 (29.7%) women were HPV16/18+ and 45 (70.3%) had a 12other hrHPV infection. Absolute risk of ≥CIN2 and ≥CIN3 in women HPV16/18+ was 71.42% (95% CI: 45.35%-88.28%) and 50.0% (95% CI: 26.8%-78.2%), respectively. In women with a 12other hrHPV type it was 21.43% (95% CI: 10.21%-39.54%) and 7.14% (95% CI: 1.98-22.64%), respectively. Absolute risk of CIN3 with HPV negative ASCUS cytology was 2.17% (95% CI:0.38%-11.33%). There were no invasive cervical cancers. Relative risk (RR) of ≥CIN2 and ≥CIN3 in women with an HPV16/18 infection compared to a 12other was 3.33 (95% CI: 1.52-7.29: p=0.003) and 7.0 (95% CI: 1.67-29.39, p=0.008), respectively.

References

The prevalence of ASC-US among women in the COMPACT study was lower than ATHENA, but similar to other Japanese studies. Similar to other global studies, absolute risk of high grade lesions was significantly higher with an HPV16/18 infection compared to a 12 other or no HPV infection. Absolute risk of ≥CIN2 in women ASCUS 12 other+ was similar to that of women HPV16/18 positive with NILM cytology in the COMPACT study, 21.43% versus 19.54%. Furthermore, while women NILM HPV16/18 had a 1.5 fold higher risk of CIN3 compared to women ASCUS 12other, it was not statistically significant. (RR, 1.54, 95% CI: 0.35-6.66, p=0.57). Prospective data from the COMPACT trial is needed to decide the most appropriated triage strategy for HPV+ women.

00461

A RISK-BASED APPROACH: CO-TESTING 34 612 WOMEN WITH CYTOLOGY AND 3-TYPE HPV MRNA TEST

09. HPV screening

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Background / Objectives

HPV DNA testing is more sensitive, but less specific than cytology. HPV DNA test cannot be used in young women due to a high positivity rate. A 3-type HPV mRNA test is more specific. We wanted to investigate if co-testing could provide better protection among all age groups; reducing false negatives and enhance risk stratification by detecting HPV mRNA genotypes 16, 18 and 45, the three most prevalent HPV types in cervical cancer.

Results

From April 2016 to December 2017, the Department of Pathology, University Hospital of North Norway, 34 612 women were co-tested with cytology and a HPV E6/E7 mRNA test detecting 16, 18 and 45 (PreTect SEE). Women were followed up until June 2018. Histologically confirmed CIN2+ were used as study endpoint.

Conclusion

At baseline, 993 (2.9%) had positive HPV mRNA, 5 297 (15.3%) had abnormal cytology (ASC-US+) and 760 (2.2%) had confirmed CIN2+ during follow-up. The PPV for CIN2+ of cytology, HPV mRNA-test and double positive (Cyt+/HPV+) were 13.3% (702/5297), 37.9% (376/993) and 49.0% (333/679). HPV mRNA positive rates in the age groups 14-24y, 25-33y, 34-49y and 50-69y were 10.1%, 6.0%, 1.8% and 0.8% and abnormal cytology rates were 38.2%, 24.0%, 15.0% and 6.8%. The detection rates of CIN2+ were 5.2%, 5.2%, 1.6% and 0.5%. The PPV for CIN2+ of cytology were 12.7%, 20.3%, 9.8%, 5.9%; HPV mRNA test 26.5%, 45.7%, 37.6%, 26.0% and double positive (Cyt+/HPV+) 33.1%, 56.9%, 49.0% and 42.5%.

References

The 3-type HPV mRNA test is more specific than cytology and holds high PPV for CIN2+ regardless of age. The low positivity rate enables HPV mRNA testing of women not eligible for HPV DNA testing. Co-testing versus cytology alone gives a significant increase in PPV for CIN2+ (49.0 % vs 13.3 %) hereby improving safety and providing important assistance for clinicians in determining patients elevated risk and need for follow-up. A risk-based approach may reduce over referrals and overtreatment.

00464

PRIMARY CERVICAL CANCER SCREENING WITH A 5-TYPE HPV E6/E7 MRNA TEST: RESULTS OF 10 YEARS FOLLOW-UP

09. HPV screening

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Background / Objectives

To assess the performance of a 5-type HPV mRNA test in primary screening for women 25-69 years. We estimated the cumulative risk of CIN3+ (%) at 42, 78 and 120 months.

Results

In 2004, 19 153 women were recruited for participation in a primary screening study with a 5-type HPV mRNA test. The HPV test targeted E6/E7 mRNA from HPV 16, 18, 31, 33 and 45 (PreTect HPV-Proofer). After excluding women with a history of abnormal cytology/CIN2+; 9 582 women were eligible for study participation. The Norwegian Cancer Registry completed follow-up of CIN2+ through December 31st 2015.

Conclusion

At study start, 27.2% of the women were 25-33 years, respective 72.8% 34-69 years old. In total, 3.2% were HPV mRNA positive, 1.5%, 0.5%, 1.2% for HPV 16, 18, and 31/33/45, respectively. The cumulative risk of CIN3+ at 42, 78 and 120 months (1, 2 and 3 screening intervals) were 11.3% (95% CI: 7.6-14.9), 16.9% (95% CI:12.5-21.2), 25.3% (95% CI: 19.0-31.5) for HPV-positive women, and 0.32% (95% CI: 0.31-0.33), 0.66% (95% CI: 0.64-0.68), and 0.99% (95% CI: 0.96-1.02) for HPV-negative women, respectively.

References

HPV mRNA positive women have a significant elevated risk of CIN3+ and can be referred directly to colposcopy and biopsy. Test negative women have low risk of CIN3+ and may return to screening. Low HPV mRNA positivity rate implies low

referral rates and reduced risk of over-treatment. A trade-off between sensitivity and specificity must be considered when decisions on HPV tests in primary screening are taken.

00582

3-TYPE HPV MRNA TEST IN DETECTION OF CIN2+ IN YOUNG WOMEN WITH NORMAL CYTOLOGY

09. HPV screening

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[5]Consultant pathologist-University Hospital of North Norway - Tromsø (Norway)

Background / Objectives

Objectives. Despite a well-established cervical cancer (CC) screening program in Norway, the incidence of CC in young women is increasing, peaking at 35 years. Twenty-five percent of all women diagnosed with CC had normal cytology within 3 years of cancer diagnosis, addressing the need of improvement of screening program to further reduce cancer incidences missed by cytology. We wanted to investigate the detection rate of CIN2+ in young women with normal cytology by using a 3-type HPV mRNA test.

Results

Methods. In 2014-2017, 2,382 women <40 years with normal cytology at Nordlandssykehuset-Bodo,Norway, were HPV-tested using a 3-type HPV E6/E7 mRNA test (PreTect SEE; direct genotyping 16, 18 and 45). Index cytology from women with a positive HPV mRNA test were rescreened. Women with revised cytological diagnoses were followed-up according national guidelines until August 2018. We used histologically confirmed CIN2+ as study endpoint.

Conclusion

Results. Overall, 2.1% (50/2,382) had positive HPV mRNA test. The cytology was revised in 52.0% (26/50); 11 ASC-US, 6 LSIL, 1 AGUS, 6 ASC-H and 2 HSIL. During follow-up, biopsy was taken from 30 women. CIN2+ was detected in 56.6 % (17/30) from women that testedHPV mRNA positive (8 CIN2 and 9 CIN3), giving a total prevalence of CIN2+ of 0.7% (17/2,382) in presumed cytology normal women.

References

Conclusions. By testing women <40 years with normal cytology with a specific 3-type HPV mRNA test, an increase in screening program sensitivity can be achieved without an excessive workload. The volume of rescreened smears is low (2.1%). The PPV for CIN2+ is high (56.6%). When more women with CIN2+ are detected and treated in the first screening round, less women will develop cervical cancer before next screening round.

00075

RNA SEQUENCING OF HUMAN PAPILLOMAVIRUS NEGATIVE INVASIVE CERVICAL CANCERS

11. Genotyping

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Background / Objectives

Although cervical cancer is known to be caused by human papillomavirus (HPV), some tumors appear to be HPV-negative by primer-based detection systems.

In a previous study, we identified and requested FFPE blocks from all cervical cancers in Sweden during 2002 to 2011 (n=4254). Out of the 2850 cancer cases with adequate HPV typing results, there were 394/2850 (13,8%) cases being “apparently HPV-negative” after being tested for HPV DNA with both PCR with MGP primers targeting L1 gene and real-time PCR with primers targeting the E7 gene. We wish to perform unbiased testing (not based on PCR or other methods requiring prior knowledge of sequences) to see which actively transcribed viruses could be found in “apparently HPV-negative” cancer cases.

Results

As a pilot study, we included six cervical specimens “apparently negative” for HPV. Cervical specimens were RNA extracted with a xylene-free method, rRNA depleted, reverse transcribed and ligated to individual adapters using the TruSeq Stranded Total RNA kit (Illumina, US). Libraries were validated, normalized to 2 nM and pooled before sequencing. Sequencing was performed in the NextSeq500 system (Illumina, US) at 151 paired-end cycles. 150 bp long quality reads were screened against the human reference genome hg19 and human reads were filtered from the data set. Fastq files for each sample, were aligned to all HPV types reference clones sequences published in the website of the International Human Papillomavirus Center (hpvcenter.se, accessed 2018-05-28).

Conclusion

3/6 samples were positive for HPV RNA, with HPV 213 (Gamma-13), HPV 197 (Gamma-24) and HPV type 16 (Alpha-9) being found in one specimen each. While HPV 197 had 3524 reads covering all HPV genes (E6, E7, E4, E2, E1, L2 and L1), the HPV 213 and HPV 16-positive specimens showed reads only mapping to their respective E1 genes.

References

In Illumina total RNA sequencing data with a median of 30 million reads per sample, HPV transcription was detected in 3/6 apparently “HPV-negative” cervical cancer specimens (negative in PCRs directed to the L1 and E7 regions). The HPV197 and HPV213 may have escaped detection due to mismatch to primers/probes in the conventional PCR-based HPV detection systems.

00062

Online platform for monitoring of cervical screening programmes in the Nordic countries

13. Screening methods

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Background / Objectives

Quality assurance and improvement of cancer screening programmes require up-to-date monitoring systems and evidence-based indicators that reflect benefits, costs and harms. [1] The NordScreen project has developed a publicly available web-based interactive application to access standardized performance and outcome indicators of cancer screening, based on up-to-date Nordic cancer screening register data. [2] Fact sheets summarising the cancer screening policies and programmes in place in all the Nordic countries and Estonia are also available on the NordScreen website.

Results

The screening data originate from population-based screening registries. The test data are available on individual level linked to personal ID number. Through a network of Nordic and Baltic screening managers, population-based individual screening data from each country were converted to standard format in situ and aggregated by an R program script for use by the NordScreen online platform. Comparability between countries is enhanced by the uniform data structure and standardized calculations. The online platform is currently based on PowerBI software by Microsoft.

Conclusion

The NordScreen collaboration has so far collated standardized indicators for test coverage, average number of tests per interval and distribution of women according to number of tests per interval. These indicators are based on 32.8 million screening

tests from 4 Nordic countries and Estonia. Interactive comparison of test coverage between countries is currently possible on-line (nordscreen.org). In 2015, the test coverage within a time interval of of 5.5 years in the age group 30–64 year-olds was between 78–84% in Iceland, Norway and Sweden whereas 70% in Finland. The application allows users to define indicator specifications interactively.

References

NordScreen is a pilot model for cross-country comparison of cancer screening. The comparison of coverage rates to national figures show that the methods produce quite similar results. The aim is to stimulate collaborative research and quality improvement in screening through freely available, interactive, and regularly updated quality indicators. The project currently includes data on cervical cancer screening and screening programmes for breast cancer and colorectal cancer will be included in coming phases.

References

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00436

p16/Ki-67 AND HPV AS TRIAGE TESTS IN ROUTINE SCREENING: CORRELATION WITH HISTOLOGY

13. Screening methods

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Background / Objectives

Annual conventional cytology (CC) is still the standard in the German cervical cancer prevention program. The sensitivity of a single CC for the detection of cervical intraepithelial neoplasia is low. High-risk HPV (HR) testing and p16/Ki-67 (CINtec® Plus, Roche Ventana, Mannheim, Germany) are valuable for the triage of borderline and low-grade cytological abnormalities. Both tests used in routine improved the sensitivity and specificity for CIN 2+ lesions. We analysed the correlation between the p16/Ki-67 and HPV status of patients before biopsy/therapy with histologically confirmed CIN 2 and 3 and invasive cervical carcinoma.

Results

All cases of a German routine lab in which histology had been performed from 2012 till 08.2018 and results of, for HR HPV DNA tests (Hybrid Capture2 ® Qiagene. Hilden, Germany till 2013 after that cobas ®, Roche Diagnostics, Mannheim, Germany) and p16/Ki-67 tests (both carried out maximally 3 months earlier) were available are reported. Histology followed colposcopically directed biopsy, conization. All HPV and p16/Ki-67 tests were made out of cervical smears taken in proprietory tubes or in Thinprep vials (PreservCyt®, Hologic, Wiesbaden, Germany) according to the manufacturers instructions. While cytology, HPV- and p16/Ki-67 tests were made at Cytomol, histology was performed in numerous pathology institutes.

Conclusion

In 5354 of 6697 (80%) CIN 2+ cases an HPV result and in 3737 (56%) cases a p16/Ki-67 result was available. For all years together in CIN 2 1246 of 1295 (96,2%), in CIN 3 3794 of 3918 (96,8%) and in cervical cancer 133 of 141 (94,3%) cases were HR HPV positive. In CIN 2 832 of 864 (96,2%), in CIN 3 2775 of 2793 (99,35%) and in cervical cancer 79 of 80 (98,75%) cases were p16/Ki-67 positive. Altogether 181 (3,3%) histologically confirmed CIN 2+ were HPV test negative, and in 51 (1,3%)

were p16/Ki-67 negative. Only 7 of 57 CIN 2+ HPV high risk test negative cases with parallel p16/Ki-67 testing were negative for both tests.

References

The large majority of histologically confirmed CIN 2 and 3 and cervical cancers were positive for HR HPV and the biomarker p16/Ki-67 when tested in cervical smears < 3 months before biopsy/therapy. These results from routine testing point to a high sensitivity of HR HPV testing for CIN 2+ and slightly higher sensitivity of p16/Ki-67 (in CIN 3 and ICC cases). Triaging with HPV and p16/Ki-67 in routine increased sensitivity and specificity for CIN 2+ and may avoid the overtreatment.

00394

MUCH LOWER RATE OF LIMITED AND INSUFFICIENT SMEARS WITH LBC (THINPREPTM) THAN WITH CONVENTIONAL CYTOLOGY - EXPERIENCE IN ROUTINE

14. Liquid based cytology

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Background / Objectives

While the sensitivity of liquid based cytology (LBC) for high grade cervical disease is still under discussion the better technical quality of its smears is much less questioned. Most of these analyses have been performed under study conditions. We therefore investigated that aspect in a large routine lab.

Results

Cytomol is one of the major cytology labs in Europe with an experience in LBC (ThinprepTM) since over 15 years. Since over ten years all LBC and conventional specimens are pre-analyzed by computer-assistance. 12 of our cytotechnicians (CTAs) were asked to qualify all routine slides they examined within two weeks with special consideration to the technical quality of the smears. Because in Germany LBC is still reserved to privately insured and self-paying patients its volume is only about 10% of all cytology cases. This is reflected in the following data.

Conclusion

The age range of the CTAs examining conventional slides was 24 to 58 years, their professional experience varied from 3 to 35 years. 11.887 slides were analyzed, the individual CTA saw between 61 and 3394 slides. Alltogether 83.63 % of them were classified as well evaluable, 14.53 % as of limited and 1.84 % as of insufficient evaluability. The reasons for that judgement were (in decreasing frequency) overlay by leucocytes and blood and/or mucus, fixation failure, mechanically alterated cells and lacking endocervical cells. The median of the percentage of the well evaluable cases was 84.11%, its range 63.16 % to 95.08 %. For the cases of limited evaluablity

the median was 15.78 %, its range 4.92 % to 29.32 % and for the smears qualified as insufficient the median was 0.51 %, its range 0 % to 7.52 %.

1.193 LBC specimens were examined by 7 CTAs whose age ranged from 40 to 58 years and whose professional experience varied from 11 to 35 years. The individual CTA saw between 60 and 382 slides. 93.30 % of them were classified as well evaluable, 5.53 % as of limited and 1.17 % as of insufficient evaluability. The reasons for that judgement were (in decreasing frequency) use of gel, cytolytic cells and low cell number. The median of the percentage of the well evaluable cases was 94.41 %, its range 87.96 % to 100 %. For the cases of limited evaluability the median was 4.20 %, its range 0 % to 11.11 % and for the smears qualified as insufficient the median was 0.93 %, its range 0 % to 2.99 %.

Together the percentage of smears with limited or insufficient technical quality was 16.38 % for conventional slides and 6.76 % for LBC.

References

In routine use LBC had a 2.42 times lower rate of smears with limited or insufficient evaluability than conventional cytology.

00202

Nine years of the SCOTTISH HPV ARCHIVE - A resource support for basic and applied HPV research

19. New technologies

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Background / Objectives

Biobanking is essential to support HPV-associated basic and clinical research. A recent survey of key opinion leaders confirmed this as a top 10 priority for HPV based research and development. Some of the key considerations for biobanking are: to ensure samples are stored and disseminated with due process of governance; ensuring samples are of the nature and quality to support contemporary, priority research; and sustainability models.

Results

The Scottish HPV Archive received government core-funding for the first five years and then has been sustained via research funding and a revenue model based on sample provision. Several permissions were sought to ensure robust and informative linkage to relevant clinical information and recently the archive was added within the Lothian NRS BioResource[1]. Access to samples is obtained through application to a multi-disciplinary archive steering committee[2].

As a dynamic archive, it is a collection of collections and includes samples from women attending routine screening in addition to research collections associated with specific inclusion criteria. Currently, the archive contains over 45,000 samples (37,613 liquid based cytology, 8,231 nucleic acid extracts and 863 self-taken vaginal swabs). Samples are annotated with HPV and vaccination status, as well as pathology information. Quality assessment is performed regularly to assess best storage conditions for viable cells, DNA, RNA and protein.

Conclusion

To date, 51 applications have been approved for use, with an increase in applications over the last two years. Requests are associated with research into HPV epidemiology (5, 9.8%), new technologies for HPV detection (20, 39.2%), validation and assessment of HPV detection assays (17, 33.3%) and basic research into HPV (9, 17.6%). The applications have been both from United Kingdom (40, 78.4%) and international partners (11, 21.6%%); and 11 (21.6%) have involved commercial collaborations. The archive has been associated with several grants and peer reviewed publications[3] with outputs disseminated at national and international microbiology and oncology meetings. A recent challenge is the increasing and understandable demand that is made on nucleic acid quality and yield (from clinical samples) to reconcile with sophisticated molecular technologies that require long reads. Our intention is to maximise/optimise processing extraction and storage conditions to enhance quality.

References

In the nine years since its establishment, the Scottish HPV Archive has proved to be a valuable resource for researchers. Our aim is to further collaborate with the international community to: establish best practice for biobanking, determine what type of samples would support research optimally and consider joined-up options for funding/sustainability.

References

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00091

A Danish Clinical Cervical Cytology Biobank. Pilot studies of sample processing and quality

20. Diagnostic procedures / management

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Background / Objectives

Using liquid-based cytology usually only a smaller portion of the collected material is used for primary diagnostics (cytology and/or HPV testing.) The residual material is stored in either uncontrolled condition or discarded. For the purpose of future diagnostics and in order to continuously monitor and evaluate new screening methods and biomarkers, a cervical cytology biobank is very valuable. The objective of this study was to identify and evaluate an efficient workflow for establishing a cervical cytology biobank with high cell yield and high quality of the stored material.

Results

The biobank will consist of residual material from liquid-based cytology samples (ThinPrep, Hologic) collected from women participating in the national screening program for cervical cancer in the uptake area of Sygehus Lillebaelt, Denmark (approx. 50,000 samples/year).

The workflow shown in figure 1 is automated using the Freedom Evo 200 robot (Tecan), and information on samples and storage is administrated by the Labware LIMS system.

Cell yield was evaluated by measuring the amount of DNA in the original ThinPrep vial compared to the yield of DNA in the biobanked sample.

As an estimate of quality biobanked samples were examined by PCR with a 600 bp amplicon and with an NGS panel (TST15 panel, Illumina). In addition, imprint of a subset of samples have been compared before and after biobanking.

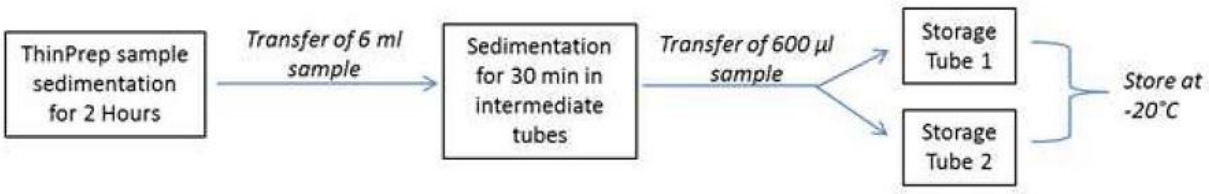
Conclusion

Based on 24 samples the DNA yield in storage tube 1+2 was on average 47% of the content in the primary tube. PCR results showed that 600 bp amplicons could be amplified for all samples, revealing high quality DNA. The DNA is also useful for NGS, as the analysis using the TST15 panel showed good quality parameters and high amplicon coverage.

A gynecological pathologist examined the imprint from samples before and after biobanking and no differences were observed, indicating that cells in the biobank are intact and could be used for analyses like IHC, FISH etc.

References

Using the presented workflow, a cytology biobank has just been initiated. Updated and further data on quality measurements of DNA, RNA and protein will be presented. The biobank holds great potential for future clinical purposes as wells as for research and quality assurance.



FC 02. Molecular markers 1

00084

TAME-SEQ: AN EFFICIENT SEQUENCING APPROACH TO CHARACTERISE HPV GENOMIC VARIABILITY AND CHROMOSOMAL INTEGRATION

01. Viral and molecular biology

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Background / Objectives

HPV genomic variability and chromosomal integration are important in the HPV-induced carcinogenic process. To uncover these genomic events in an HPV infection, we have developed an innovative and cost-effective sequencing approach named TaME-seq (tagmentation-assisted multiplex PCR enrichment sequencing). TaME-seq combines tagmentation and multiplex PCR enrichment for simultaneous analysis of HPV variation and chromosomal integration, and it can also be adapted to other viruses.

Results

For method validation, cell lines (n=4), plasmids (n=3), and HPV16, 18, 31, 33 and 45 positive clinical samples (n=21) were analysed. Samples were subjected to tagmentation using Nextera DNA library prep kit. Following tagmentation, target enrichment was performed by multiplex PCR using HPV primers and a combination of i7 index primers (adapted from Kozich et al., 2013) and i5 index primers from the Nextera index kit. Sequencing was performed on the Illumina MiSeq or Hiseq2500 platform. Data was analysed by an in-house bioinformatics pipeline.

Conclusion

Results showed deep HPV genome-wide sequencing coverage and high on-target read mapping. Chromosomal integration breakpoints and large deletions were identified in HPV positive cell lines and in one clinical sample. A high number of low frequency variants was observed throughout the HPV genome in all the samples.

References

In contrast to other approaches, TaME-seq proved to be highly efficient in HPV target enrichment, leading to reduced sequencing costs. The unique design of TaME-seq enables simultaneous analysis of HPV variation and chromosomal integration. Comprehensive studies on HPV intra-host variability generated during a persistent infection will improve our understanding of viral carcinogenesis. Efficient identification of both HPV variability and integration sites will be important for the study of HPV evolution and adaptability and may be an important tool for use in cervical cancer diagnostics.

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00095

HUMAN PAPILLOMAVIRUS TYPE 16 GENOMIC VARIATION IN WOMEN WITH SUBSEQUENT IN SITU OR INVASIVE CERVICAL CANCER: PROSPECTIVE POPULATION-BASED STUDY

02. Epidemiology and natural history

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Background / Objectives

HPV genomic variation may be involved in viral carcinogenesis.

Results

In a national register-based nested case-control study, we retrieved archival smears from baseline cytologically normal women who later developed cancer in situ (CIS), squamous cervical cancer (SCC) or remained free of disease. These smears were previously HPV-tested by PCR and HPV16 was the strongest risk factor. We now used the Illumina NextSeq platform to sequence HPV16 genomes in cervical smears from 242 women who later developed CIS/CIN3 (n=134), SCC (n=92) or remained healthy (n=16).

Conclusion

The median sequence depth per sample was high (11288x). For 218/242 samples (>90%), we covered ≥80% of the complete HPV16 genome with sequencing median depths of >200x. We identified a wide range of unique isolates and 343 novel SNPs across the 218 samples. Most women (97%) had HPV16 lineage A infection, with the sublineages being A1 (66.1%), A2 (28.9%) and A4 (1.8%), respectively. The least variable gene was the E7 (3.4% variability), where 170/204 case women (83%) displayed a fully conserved sequence. There were no obvious differences by disease outcome (CIS or SCC).

References

We found a high number of novel SNPs. The E7 gene was hypovariable both among women developing CIN3/CIS and SCC.

00414

CONCORDANCE OF HPV16 VARIANTS BETWEEN HETEROSEXUAL PARTNERS IN THE HITCH COHORT STUDY

02. Epidemiology and natural history

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Background / Objectives

Molecular variants from some phylogenetic branches of HPV16 are more likely to cause cervical lesions than others. Data on transmission dynamics of variants are lacking; we studied concordance of HPV16 variants within individuals and between sexually active couples.

Results

We used data from HITCH, a prospective cohort study of recently formed, heterosexual couples (women aged 18-24, men 18+) in Montreal between 2005 and 2013. Genital, oral, and hand samples were collected at clinic visits for up to two years. Samples were tested for HPV DNA by Linear Array genotyping PCR assays; HPV16-positive samples were analyzed by PCR sequencing using primers flanking a segment of the long control region. We conducted cross-sectional analyses of HPV16 variants at the same visit. Wilcoxon rank-sum tests were used to calculate differences in viral loads.

Conclusion

Of 674 samples positive for HPV16, we could study intratypic variation in 584 (86.6%) samples from 201 subjects. Invalid samples had a lower viral load than valid samples (P<0.001). We identified 33 variants. Most (n=176, 87.6%) HPV16-positive subjects had only one variant during HITCH; we identified a maximum of three variants in four participants. All but one (99.8%) sample contained one variant.

Within individuals, genital-hand concordance of HPV16 variants was significantly higher than by chance; the observed/expected (O/E) ratio was 6.6 (95% confidence interval (CI): 4.0-10.2) for women, and 7.8 (95%CI 4.3-13.1) for men. All men with a detected HPV16 variant in hand samples had the same variant in penile samples (n=14). In women, hand-to-genital concordance rate was 87.0% (n=25). Intra-individual oral-genital concordance was only increased in men (O/E ratio=4.2, 95%CI: 1.1-10.8), while oral-hand concordance for HPV16 variants was neither increased in men nor women.

Between sexual partners, genital-genital concordance of HPV16 variants was 60.8% (O/E ratio=4.4, 95%CI: 3.4-5.6). Hand-hand (48.6% concordance, O/E ratio=10.2, 95%CI: 4.7-19.4) and hand-genital (concordance range: 25.0%-86.7%; O/E ratios 6.8 (95%CI: 3.6-11.6) and 5.3 (95%CI: 2.9-8.9) for male hand-female genital and female hand-male genital concordance, respectively) variant concordance rates were increased. However, oral-genital, oral-hand, and oral-oral concordance between partners were comparable to concordance rates expected by chance (concordance range: 0.0%-42.9%).

References

Within young, sexually active, heterosexual couples included in HITCH, we found a high genital-genital, genital-hand, and hand-hand concordance of HPV16 variants. Concordance of HPV16 variants in the oral cavity and other body sites was low.

00494

CHARACTERIZATION OF T-CELL SURFACE MARKERS IN PERSISTENT HPV INFECTED MOTHERS AND THEIR CHILDREN

04. Immunology

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Background / Objectives

The host adaptive immune system plays a central role in preventing persistent HPV infections. Especially effectively functioning T-cells are important, but characterization of T-cell subpopulations between different HPV infection outcomes are not well known. The aim of this study was to characterize the T-cell surface markers associated with persistent genital and oral HPV16 infection among mothers' and their children in the Finnish Family HPV Study (FFHPV).

Results

FFHPV study was originally designed to clarify the dynamics of HPV transmission infections within regular 329 Finnish families. For this present study a subgroup of 42 mothers and their children (n=28) with a 14-year follow-up where evaluated according to the mothers' HPV infection outcome. The following groups of mothers and children were generated: 1) mothers who developed an incident CIN (mothers n=10, children n=10), 2) mothers who had a persistent oral HPV16 infection (mothers n=7, children n=7), 3) mothers who tested always oral HPV16 DNA negative (mothers n=5, children n=3) and 4) mothers who tested always genital HPV16 DNA negative (mothers n=20, children n=8). In addition to the lymphocyte stimulation test (LST) with fresh isolated peripheral blood mononuclear cells (PBMCs) to determine proliferation and cytokine production, the cryopreserved PBMCs were thawed and subjected to phenotypic flow cytometric analysis using antibodies directed to CD3,

CD4, CD8, CD25, CD27, CD38, CD45RA, CD45RO, CD57, CD69, CCR7 and HLA-DR.

Conclusion

The HPV16 E2 and E6 specific lymphocyte proliferation showed to be less common among persistent oral or genital HPV16 infected mothers than HPV16 negative mothers, while among children of HPV16 CIN mothers the specific proliferation was very common and offers possible protection for future HPV16 infections. The levels of IFN-γ ($p=0.014$) and IL-5 ($p=0.040$) was lower in mothers with oral HPV16 DNA positivity and the level of HPV16 E6-specific IL17 ($p=0.035$) was lower in mothers with CIN compared to controls. Analyses of the circulating T-cells, focusing on activation markers and memory markers, are currently ongoing and these results will be compared between the study groups.

References

HPV-specific responses detected in blood of mothers is related to those mothers who have a persistent infection and therefore merely a measure for the presence and visibility of the virus while detecting proliferating responses in their children provides a possible protection for future HPV infections. Characterization of the T-cell response by flow cytometry is expected to reveal T-cell subsets which are correlating with these different groups of mothers and their children.

00382

ASSOCIATION BETWEEN INTEGRATION OF HIGH-RISK HPV GENOMES, DETECTED BY MOLECULAR COMBING, AND THE SEVERITY AND/OR CLINICAL OUTCOME OF CERVICAL LESIONS.

08. HPV testing

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Background / Objectives

Background : Integration of the high-risk Human Papilloma Virus (HPV) in the cell genome is considered to be a key event in the development of cervical cancer and as one of its most important risk factor. Detecting HPV integration may therefore provide a useful marker for the identification of high-grade lesions and lesions at risk of progression. Molecular combing associated to specific Genomic Morse Code (GMC) is a powerful and innovative approach that allow accurate detection and quantification of integrated HPV sequence into the host genome.

Objectives : The aim of the EXPL-HPV-002 study is to evaluate the integration of 14 high-risk HPV as a biomarker of the severity and the progression of cervical lesions. Such a «triage biomarker» would help to reduce the number of unnecessary colposcopies, to avoid over-treatment of lesions that spontaneously regress and to better target the lesions requiring treatment.

Results

Methods : EXPL-HPV-002 is a prospective study conducted in 2 clinical sites in Czech republic. So far, 688 patients aged 25-65, referred to colposcopy after an abnormal Pap-smear, were enrolled in the study. Among them 60% were found HPV high-risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).

The study is divided in 2 phases : (1) a transversal phase using data collected at first visit (colposcopy images +/- histology, pap-smear for HPV genotyping and molecular combing) to study the association between HPV integration status versus colposcopy and histology grades. (2) a longitudinal phase using data collected in follow-up visits : cytology at 6, 18 and 30 months and colposcopy +/- histology at 12, 24 and 36

months. A pap-smear collected at 12, 24 and 36 months allows to perform genotyping and molecular combing. HPV integration status is analyzed in comparison with the evolution of lesions, viral clearance and HPV genotype.

HPV genotyping and molecular combing are performed in central laboratories, histology data are reviewed by central reading.

References

Conclusions : The transversal phase of the clinical study is achieved while the longitudinal phase data collection is still ongoing. Results of the diagnostic phase show that the HPV integration monitored by Genomic Vision’s technology is a reliable biomarker that can significantly differentiate normal subjects from women with a risk to develop precancerous lesions or cancer. Preliminary results on prognostic value of the test will be presented as well.

00002

CKAP2 EXPRESSION SERVES AS A NOVEL POOR PROGNOSTIC FACTOR IN CERVICAL CARCINOMA

12. Molecular markers

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Background / Objectives

To study the expression level of cytoskeleton-associated protein 2 (CKAP2) in cervical cancer tissues, and to analyze the relationship between abnormal expression of CKAP2 and clinicopathological factors and prognosis of cervical cancer.

Results

We first screened CKAP2 as a new candidate oncogene in two independent data sets (TCGA and gse27678). Immunohistochemistry, RT-PCR and Western blot were then used to verify the expression of CKAP2 in cervical cancer tissues, which association with clinical features was further analyzed by statistical method.

Conclusion

The expression of CKAP2 was significantly upregulated in cervical carcinoma tissues when compared with adjacent normal counterparts. Then clinical characteristics of human cervical carcinoma tissues were further classified into the high-CKAP2 group (n= 125) and low-CKAP2 group (n= 122) using the median expression value of CKAP2 as the cutoff point. The results showed that increased CKAP2 expression was significantly correlated with age, FIGO stage, lymph node metastasis, recurrence and tumor size, but not other clinical characteristics. The survival time of cervical carcinoma patients showed that patients with under-expressed CKAP2 expression notably lived longer than patients with over-expressed CKAP2 expression. We next performed univariate and multivariate analysis of prognostic factors for overall survival with the Cox regression model. We identified three prognostic factors, including FIGO stage, Lymph node metastasis and CKAP2 expression, can served as independent prognostic factors for poor overall survival.

References

In conclusion, our findings demonstrated that CKAP2 was overexpressed and served as an independent biomarker for poor prognosis in cervical carcinoma.

00243

CO-EXPRESSION OF HPV E6, E7 MRNA AND PD-L1 IN CERVICAL CYTOLOGY SAMPLES

12. Molecular markers

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Background / Objectives

HPV infection in most women is transient and clears over time. For others, the virus is persistent and can lead to pre-cancerous lesions and subsequently cervical cancer. The relatively high regression rate of cervical intraepithelial lesions (CIN) has similarly been attributed to engagement of the immune response directed against neoplastic cells. Recent advances in immuno-oncology have shown the dramatic effects of PD-1/PD-L1 inhibitors in epithelial tumors including squamous cell carcinoma and adenocarcinoma, the major cancer subtypes in the female genital tract. Here, we present a novel assay that combines RNA in situ hybridization for HPV E6, E7 mRNA, cell cycle analysis, and PD-L1 cell surface staining on epithelial cells in liquid-based cervical cytology specimens.

Results

Forty-six residual cervical cytology specimens were obtained for this study: 25 HPV DNA-, 12 LSIL HPV DNA+, and 9 HSIL HPV DNA+. Samples underwent in-situ hybridization with E6,E7 mRNA probes and a cell cycle dye. Anti-PD-L1 antibody was added following in-situ hybridization. Samples were collected on a Beckman Coulter CytoFLEX. Samples were deemed positive or negative for E6,E7 and Post G1 expression by a dual cut-off of 3.15%. PD-L1 expression was determined based on a cut-off of 2%.

Conclusion

Sample	Positive %E6,E7 and Post G1	Positive %PD-L1	% Dual E6,E7 and PD-L1
HPV DNA-	24% (6 of 25)	24% (6 of 25)	83% (5 of 6)
LSIL	50% (6 of 12)	25% (3 of 12)	50% (3 of 6)
HSIL	33% (3 of 9)	11% (1 of 9)	33% (1 of 3)

References

In this study we show dual E6,E7 and PD-L1 expression on the same sample. HPV and PD-L1 expression on cell by cell basis is not currently available in a single test by any other method. It appears PD-L1 expression decreases in high grade lesions indicative of immune surveillance which could support therapeutic options.

00254

The inverse relation between expression of pan-HPV E4 and methylation markers FAM19A4/miR124-2 in the identification of productive and transforming cervical intraepithelial neoplasia

12. Molecular markers

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Background / Objectives

To identify productive and transforming cervical intraepithelial neoplasia using HPV E4 and p16 immunohistochemistry; to determine the methylation positivity as detected on cervical smear, of E4/p16-identified transforming lesions.

Results

Women whose inclusion smear was tested for FAM19A4/miR124-2 hypermethylation and who had a worst lesion of CIN1-3 detected on biopsy were selected from a prospective follow-up study (EVAH study). Biopsies were cut and stained for H/E, E4 and $p16^{INK4a}$. Lesions of which the diagnosis on the original section differed from the diagnosis on the new section were excluded; 188 remained. Women with initial E4 positive and E4 negative lesions were compared for methylation status in the inclusion smear and grade of p16 stain of the initial worst lesion.

Conclusion

179 biopsies were included: 58 CIN1, 78 CIN2 and 43 CIN3. 44.8% of CIN1, 19.2% of CIN2 and 4.7% of CIN3 lesions were E4 positive. A cervical smear positive for FAM19A4/miR124-2 was found in 22.4% of women with CIN1, 43.6% CIN2 and 72.1% CIN3. We found a significantly higher proportion of E4 positivity of the worst lesion present in women with a methylation- smear (30.7% E4+) compared to a methylation+ smear (15.4% E4+) ($p=0.017$, $r=-0.178$). 69.8% of E4+ lesions showed p16 in ≥2/3 of the epithelium.

References

E4 positive lesions are lesions in the productive phase of the HPV lifecycle and most likely relatively recent infections as indicated by the negative correlation with methylation status. Extensive diffuse p16 expression did not indicate a non-productive, fully transformed lesion.

00338

INTER-LABORATORY REPRODUCIBILITY OF THE P16INK4A/KI-67 DUAL STAINING IN HPV POSITIVE WOMEN FROM THE NTCC2 STUDY

12. Molecular markers

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Background / Objectives

New Technologies for Cervical Cancer 2 (NTCC2) is a large randomized clinical trial within organized cervical screening programs in Italy using HPV-DNA as primary screening test. The aim of NTCC2 is the evaluation of new biomarkers as triage test of HPV-DNA positivity, in comparison to cytology. In particular, we are evaluating Aptima HPV Assay (Hologic) for HPV E6-E7 mRNA, and CINTec PLUS Assay (Roche Diagnostics) for the immunocytochemical dual-staining of p16ink4a and Ki-67 proteins. In a previous study the p16ink4a/Ki-67 dual staining showed a good reproducibility between readers from nine different laboratories on selected immunostained slides, confirming its robustness, which is a necessary requisite for introduction in cervical cancer screening (1). In this study we assessed the inter-laboratory reproducibility of the test interpretation among the samples enrolled in the NTCC2 study.

Results

ThinPrep liquid based cytology slides from baseline HPV-DNA positive women, were immunostained by CINtec® PLUS Assay in four centres and were interpreted in seven different centres involved in cervical cancer screening and/or in cervical cancer research. Immunostaining results were classified as positive (at least one double stained cell), negative, or inadequate. Each immunostained slide was analyzed and scored independently by three different laboratories giving a total of 4027 reports. To evaluate inter-laboratory interpretation reproducibility, kappa values for multiple raters were reported for the overall agreement and ninety-five percent confidence intervals (95%CI) were calculated, using the bootstrap method with bias correction.

Conclusion

Overall, 454 out of the 4027 reports were inadequate (11.2%), mainly because of scant cellularity or staining decay. The overall concordance for adequacy was poor (kappa value 0.155, 95%CI: 0.106-0.213). However, considering only the consecutive first and second interpretations, the kappa value increased to 0.425 (95%CI 0.325-0.526). When we took into consideration only the 3573 evaluable reports, we observed 1261 positive (35.3%) and 2312 negative readings (64.7%), with a good concordance for positivity (kappa value 0.623, 95%CI 0.586-0.665). Also in this case, considering only the first and the second reports the kappa value rose to 0.746 (95%CI 0.705-0.788).

References

The dual-staining for p16ink4a and Ki-67 showed a good reproducibility for positivity, which is a necessary prerequisite for adoption as a triage test in cervical cancer screening programs with HPV-DNA as primary test.

References

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00456

CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER: A GENOME WIDE ASSOCIATION STUDY (GWAS) OF UK BIOBANK AND NORTHERN FINNISH BIRTH COHORTS (NFBC66)

12. Molecular markers

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Background / Objectives

Persistent infection with high-risk human papillomavirus (HPV) is causally associated with cervical cancer. However, only ~1% of women with HPV infection progress to cervical neoplasia (CIN). It is estimated that genetic heritability may explain 25-30% of total variation in liability for cervical cancer. Common genetic variants have been detected in HLA (Human Leukocyte Antigen) regions responsible for the immune response, but this is not well understood. We conducted a genome-wide association study, in two cohorts, to identify underlying genetic risk variants which might predispose to CIN and cervical cancer.

Results

Using Northern Finland Birth Cohort 1966 (NFBC66) and Finnish nationwide registers we identified 365 women with CIN/cervical cancer and 1678 controls without a history of any cytological abnormalities. Using UK Biobank data and United Kingdom (UK) national cancer registries we identified 6378 women with CIN3/cervical cancer and 198,441 controls, this represents the largest cervical cancer GWAS to date. We conducted genome wide analyses for CIN or cervical cancer first in NFBC66 followed by UK Biobank.

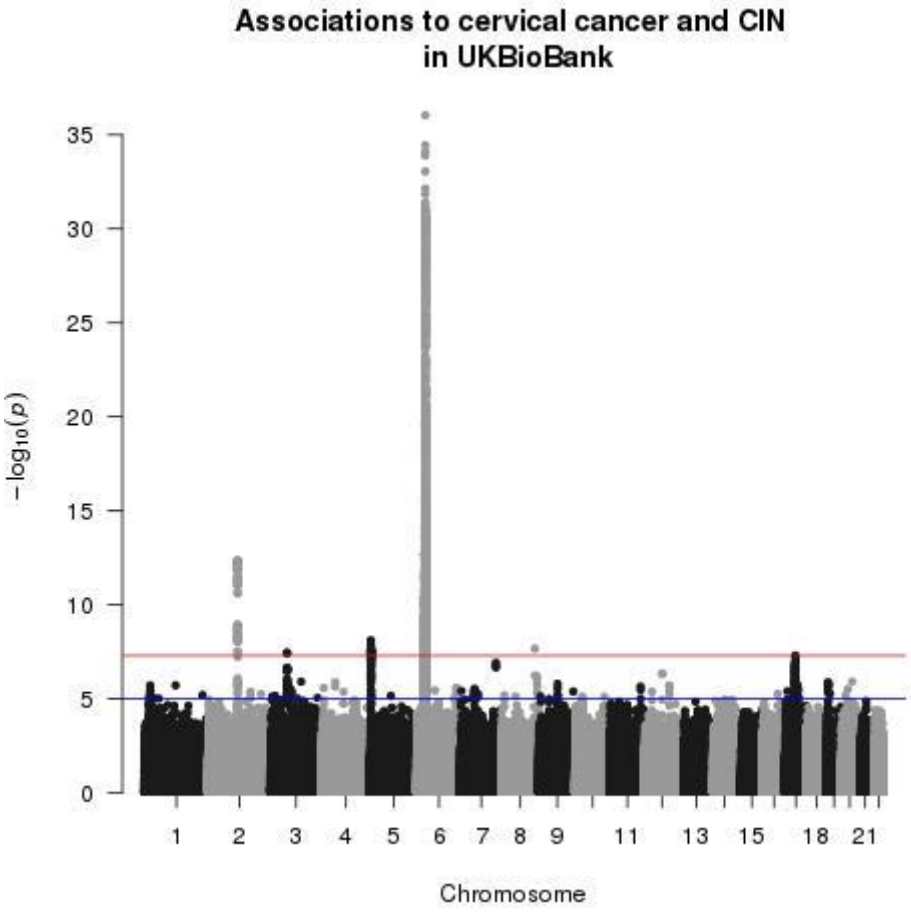
Conclusion

In the NFBC66 cohort we identified SNPs ($p<5x10E-8$) associated with increased risk of CIN or cervical cancer. Two of the top variants were associated with three protein-

coding genes at the same locus: PIBF1, BORA and MZT1, all with roles in mitotic cell division and/or cancer development. In the first UK Biobank iteration we have identified potential SNPs (p<5x10E-8) associated with CIN3/cervical cancer, with a large number of significant loci residing within Chromosomes 2 and 6 (Figure 1). Independent loci in the Major Histocompatibility Complex (MHC) region at 6p21.3 were associated with CIN3/cervical cancer, including loci adjacent to the MHC class 1 polypeptide-related sequence A gene (MICA) and HLA-DRB1, which replicates previously reported associations from published GWAS.

References

We observed genetic variants significantly associated with CIN or cervical cancer in both cohorts. Loci within the MHC may affect susceptibility to development of CIN3/cervical cancer through altered immune responses. We will next undertake fine-mapping within the UK Biobank cohort, to determine replication of NFBC66 findings and further classify any novel causal variants that may explain the estimated genetic susceptibility to cervical cancer.



00539

BIOMARKER DISCOVERY FOR IN VIVO IMAGING OF CERVICAL PRECANCERS

12. Molecular markers

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Background / Objectives

Due to the low specificity of HPV DNA testing, triage testing for positively screened women is required to reduce overtreatment harms, but current triage options in low income settings are limited. Specific biomarkers that could be readily detected during the patient encounter through in vivo imaging present a novel promising triage strategy. We used a gene-expression based biomarker discovery approach for development of in vivo imaging markers.

Results

The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) recruited women referred for colposcopy with abnormal screening results. Gene expression levels were determined in mRNA microarrays of SUCCEED tissue from 128 patients at all stages of progression to cervical cancer, and differential expression of genes compared between cervical intraepithelial neoplasia grade 3 (CIN3) and combined CIN1/normal tissues. Candidate biomarkers with nominally significant p-values (<0.01) and higher expression in CIN3 (fold-change >2) were investigated for membrane localization and enzymatic activity. Initial validation of the top candidate genes through immunofluorescence staining of cervix tissue microarrays was followed by immunohistochemical validation of the most promising candidates in full tissue slides from SUCCEED.

Conclusion

Using these criteria, we found 48 potentially plasma membrane-bound proteins that could be amenable to in vivo staining and visualization. Candidates were evaluated for likelihood of membrane localization, enzymatic activity that would facilitate the development of an in vivo imaging probe, availability of validated antibodies, and evidence of cancer-associated alterations in protein expression or function. Candidates were prioritized, and 11 high priority proteins were stained in cervix tissue microarrays that included six cancers and six adjacent normal tissue cores. MUC4 exhibited strong membrane staining in all the cancers and negative to weak staining in normal epithelium samples. MUC1 exhibited low to moderate membrane staining in normal epithelium and moderate to strong staining in cancer. These two candidates were selected for further validation through immunohistochemical staining of SUCCEED tissue slides using conventional histology evaluation and automated image analysis. This effort is currently under way, which will be followed by the investigation of the in vivo imaging potential of validated candidates using both antibody-based and enzyme-activated optical imaging methods.

References

The discovery of membrane biomarkers of cervical cancer and precancerous lesions may enable the development of specific, sensitive, low cost in vivo detection tests for prevalent precancers.

FC 03. Vulvar and penile HPV diseases

00036

PREVALENCE OF HPV IN FRESH TISSUE OF PENILE CANCER

02. Epidemiology and natural history

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Background / Objectives

The prevalence of HPV in penile cancer have been shown to be around 47 %, ranging between 24% and 82 % (1, 2). Analysis has mostly been performed on formalin embedded tissue, except in 74 cases of fresh tissue (1). The large variation in HPV-prevalence is most likely due to different histological type of tumors and different methods for HPV analysis. Our aim was to determine the prevalence of HPV in fresh tissue of invasive penile cancer cases and from nonmalignant penile controls.

Results

Fresh tissue from consecutive invasive penile cancer cases operated in Skane University Hospital from June 22, 2015 through June 1st 2018 was biopsied immediately after arrival at the Department of Pathology. Controls were men circumcised of nonmalignant reasons, with biopsies taken in the operation room. All penile cancer cases and all controls filled in a survey regarding general diseases, medication, former symptoms, diseases and surgical procedures on penis and number of sexual partners. Each 2 mm biopsy was put in RNAlater (Ambion) and transferred to 1 mL GITS-solution (4M guanidinium thiocyanate, 22mM NaCitrate and 5% Sarcosyl (N-Lauroylsarcosine sodium salt) and 1% mercaptoethanol) and incubated at room temperature overnight. Then DNA was extracted with the Total NA-kit (Roche, Stockholm, Sweden) using MagNA Pure LC (200 uL input and 100 uL output). Sample adequacy was assessed by testing 5 uL of the sample for the human beta globin gene with a real-time PCR. Simultaneous identification of 40 genital HPV types were carried out by modified general primer polymerase chain reaction (MGP-PCR) and subsequent Luminex analysis in a 25 uL reaction, containing 5 uL of extracted material. The Luminex assay included probes for HPV types 6, 11, 16, 18,

26, 30, 31, 33, 35, 39, 40, 42, 43, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68 (a and b), 69, 70, 73, 74, 81, 82, 83, 85, 86, 87, 89, 90, 91 and 114.

Conclusion

Hitherto, 83 men with invasive penile cancer have been included and 214 controls without penile cancer. Mean age of men with invasive penile cancer were 68.8 years (range 28-87 years) and for controls 46 years (range 19-90 years). Of penile cancer cases, 42.2 % (35/83) had HPV in the tumour. High risk HPV types were found in 41.0 % (34/83), where HPV 16 was present among 32.5 % (27/83). In 6.0 % (5/83) multiple HPV types existed. Among the controls, 13.6 % (29/214) had HPV in the circumcised tissue. High risk HPV types were found in 6.1 % (13/214), where HPV 16 was present 1.4 % (3/214). In 3.7 % (8/214) of controls, multiple HPV types were present.

References

HPV is more common in invasive penile cancer than in non-malignant controls ($P<0.0001$). HPV 16 is the predominant HPV type.

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00367

PREVALENCE AND DETERMINANTS OF HUMAN PAPILLOMAVIRUS IN MEN AND TRANSGENDER WOMEN WHO ARE SEX WORKERS: SWEETIE STUDY

02. Epidemiology and natural history

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Background / Objectives

Men and transgender women (TGW) who are sex workers are an exposed and vulnerable population for Sexually Transmitted Infections (STI), of difficult access, resulting in a lack of information about prevalence and determinants of STIs in general and Human papillomavirus (HPV) in particular. To estimate the anogenital and oral HPV prevalence and determinants in men and TGW who report to be sex workers.

Results

Men and TGW aged ≥18 residents in Barcelona are enrolled in a cross-sectional study conducted in collaboration with local non-governmental organizations, STOP SIDA. Demographic and behavioral characteristics are assessed by questionnaire, and anal, perianal, penis, urine and oral samples were collected for HPV testing and genotyping.

Conclusion

From a total of 37 participants, 25 were TGW (recruitment is currently ongoing). Average age was 33 years and most participants were foreigners (97.4%), mainly from South America. 23% reported to be HIV-positive and 35.1% had another active STI. The prevalence of HPV was 91.6% in anal, 12.9% in oral and 6% in urine samples. Many participants were unfamiliar with HPV vaccination, but 87.1% expressed positive attitudes for vaccination. We estimate to collect a total of 450 samples from 90 participants until the end of the recruitment phase (July, 2018). HPV results from all patients and all locations will be presented at the IPVC 2018.

References

The prevalence of HPV infections is higher in this population than general population, mainly in anal and oral sites. Specific HPV vaccine programs addressed to this population should be considered.

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00361

MEN, THE FORGOTTEN VICTIMS FOR HPV DIAGNOSIS

08. HPV testing

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Background / Objectives

In men, high risk (hr) types can induce penile or rectal intraepithelial neoplasias or penile cancer, while low risk (lr) HPV types, may cause genital warts or atypical genital or perigenital lesions. Aim of the retrospective study in men was to evaluate the results of lr- and hr HPV genotyping in male samples, collected at or sent to the Outpatients Centre for STI Diagnosis in Vienna.

Results

Out of 7032 patients tested for HPV between January and June 2018, 746 (10.6%) samples were collected mainly from the penile (46%), perigenital (26%), and anorectal (10%) area, respectivley, from male individuals with an average of 37 years. Patients were either referred to the Outpatients centre for HPV diagnosis or samples were sent and examined for the presence of HPV high- and low-risk genotypes by using the PapilloCheck®. This is a microarray-based assay for the detection and identification of 18 hr HPV and 6 lr HPV types, based on the detection, amplification, and genotyping of a 350pb fragment of the viral E1 gene.

Conclusion

The main indications for testing HPV, was the presence of genital warts (37.4%), a suspicious HPV infection (38.1%), and partner control (4.6%). Of the 420 HPV positve samples (57%), 46,7% were lrHPV, 25.2% hrHPV, and 28,1% both, lr and hrHPV positive.

The most prevalent lr-genotypes were HPV 6 (24.6%), 11 (4%) and 42 (8.8%), respectively, and hr-genotypes were HPV 16 (10.3%), 51 (6.1%) and 56 (6%), respectively. In men with genital warts, 78% were HPV positive including lrHPV only (47.7%), hr HPV only (12,5%) or a mixed infection (17.8%). Serotyping showed HPV6 as the most prevalent lr genotype (37.8%) followed by other lr-HPV (24%). Among hr genotypes, HPV 16 (9.5%) was the most common one. While all men after treatment of genital warts were lr HPV negative, still 14.3% were hr HPV positive. In

men, tested due to contact tracing, either lr HPV or hr HPV were positive in 15.2%, respectively, and in 23.9% harboring both, lr and hr HPV.

References

In men with genital warts the high prevalence of HPV 6 was confirmed. However, also hr HPV, or a coinfection with hr HPV were detected in about one third of men with genital warts. In almost half of the men with suspicious HPV infection HPV diagnosis could be confirmed. The high percentage of hr HPV types either present as single or mixed infections should be considered for further controls in men and demonstrates the need for HPV diagnosis in men.

00171

DNA METHYLATION MARKERS FOR RISK STRATIFICATION OF VULVAR INTRAEPITHELIAL NEOPLASIA

24. Vulvar diseases and neoplasia

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Background / Objectives

High-grade vulvar intraepithelial neoplasia (VIN) is the precancerous state of vulvar squamous cell carcinoma (VSCC). Only a minority of VINs progress to cancer, indicating a heterogeneous disease. Current clinical and histological classifications are insufficient to predict the cancer risk. Consequently, affected women are treated similarly with mutilating interventions. Hence, there is a clinical need for objective biomarkers reflecting the cancer risk. In this study we assessed the potential value of DNA methylation markers for risk stratification of VIN.

Results

A series of 200 FFPE specimens, including normal vulva samples (controls), VIN cases and VSCC cases were included in this study. Of the VIN cases, VIN with associated VSCC (VIN with VSCC, i.e. VIN adjacent to VSCC or development of VSCC in the follow-up) and VIN without associated VSCC (VIN without VSCC, i.e. VIN without concurrent VSCC and without development of VSCC during at least ten years of follow-up) were included. Samples were tested for p16INK4a immunohistochemistry and for HPV DNA to define the HPV status. Multiplexed quantitative methylation-specific PCR assays were performed on nine candidate methylation markers to analyse differential methylation.

Conclusion

In both HPV-negative and -positive cases, methylation levels were found to be increased in both VSCC and VIN with VSCC, compared to controls and VIN without VSCC. Comparison of HPV-positive VIN without VSCC and VIN with VSCC, yielded a number of methylation markers with an area under the curve (AUC) > 0.8.

References

Our results show that vulvar carcinogenesis is associated with increased methylation of (candidate) tumour suppressor genes. We identified multiple methylation markers for risk stratification of VIN lesions, which are promising for tailored management in affected women.

00301

HISTOLOGICAL CHARACTERISTICS AND OVERALL SURVIVAL OF HPV ASSOCIATED AND INDEPENDENT SQUAMOUS CELL CARCINOMA OF THE VULVA: A RETROSPECTIVE STUDY

24. Vulvar diseases and neoplasia

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Background / Objectives

The presence or absence of HPV separates vulvar squamous cell carcinoma (VSCC) into two distinct molecular and clinicopathological entities. Studies on histological and survival characteristics present discordant results. We assessed the impact of HPV presence in the histological characteristics and the overall survival (OS) in a cohort of VSCC.

Results

We report 93 cases of VSCC with HPV status, clinical, histological and prognosis data diagnosed over a period of 14 years (2002 to 2016). HPV DNA detection was done using SPF-10 PCR/ DEIA/LIPA v2 system. Kaplan-Meier estimator and multivariable Cox regression analysis controlling for FIGO stage and age were used.

Conclusion

The median age was 74 years (range 28-96). Patients with HPV associated tumours were older (median 78 vs 71). The mean follow-up time in this cohort was 3.6 years (range <1 to 11.4 years). HPV status was determined in all, 64 HPV-negative, 29 HPV-positive, of which 11 HPV16-positive. Tumours were histologically classified as keratinizing (78%) and nonkeratinizing (14%), basaloid (5%) and hybrid (2%). 55% of the tumours were moderately differentiated, the mean tumour thickness was 34 mm (range 1-121mm). Lymph node metastasis was present in 40% of the cases and the mean lymph node metastasis size was 10.3 mm (range 0.4-39mm). FIGO stage was I in 47%, II in 10% and III in 43% of the cases. Patients were initially treated with surgery (46%), radiotherapy (45%) and chemotherapy (9%) and 37% of the patients died of the disease. HPV associated tumours were more likely to have koilocytotic

change (p<0.01). The invasive front, inflammatory infiltrate, lymphovascular space invasion, perineural invasion, positive lymph nodes and positive margins for invasive tumour were not significantly different between the two groups. No differences were found between HPV-positive and -negative tumours regarding OS (hazard ratio (HR) =1.08, 95% CI=1.21-4,17, 0.56-2.06 p=0.82). Patients who underwent surgery had superior OS (HR=0.51, 95% CI=0.26-0.99 p=0.04) and lymph node metastasis size ≥ 5mm was associated with a statistically significant inferior OS (HR=1.88, 95% CI=1.22-2.92 p=0.004).

References

Although HPV associated tumours were more likely to have koilocytotic-like change, histological criteria did not allow differentiation between HPV associated and independent VSCC. No differences in survival were observed between HPV -positive and -negative tumours. Patients who underwent surgery had a superior OS compared to other treatments and in patients with lymph nodes metastasis ≥ 5mm the OS was inferior.

00308

VULVAR INTRAEPITHELIAL NEOPLASIA: INCIDENCE AND LONG TERM RISK OF VULVAR SQUAMOUS CELL CARCINOMA

24. Vulvar diseases and neoplasia

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Background / Objectives

Given the heterogeneity of vulvar carcinogenesis, the incidence of vulvar intraepithelial neoplasia (VIN) and the subsequent cancer risk is ambiguous. Human Papillomavirus (HPV) associated VIN accounts for more than 90% of all high-grade VIN, while HPV-induced vulvar squamous cell carcinomas (VSCC) only account for 25% of all VSCCs. To optimize monitoring and clinical care of women with VIN, this study aimed to obtain knowledge about both the incidence of VIN and the subsequent cancer risk in affected women.

Results

The PALGA database, the Dutch Pathology Registry, enabled us to obtain long-term follow-up data (up to 2018) from a large historical cohort of women with VSCC, VIN and lichen sclerosus (LS) diagnosed between 1991 and 2011.

Conclusion

: In our cohort, 1,147 women were diagnosed with VIN with an incidence rate of 3.8 cases per 100,000 woman-years. Between 1991 and 2011 the incidence of VIN increased with 67%. Although most women diagnosed with VIN were between 35 and 55 years of age, the incidence rate of VIN peaked in women ≥ 70 years. This peak at higher age is explained by the fact that the presence of concurrent VIN and VSCC increases with age. The cumulative incidence of VSCC in women with VIN was 13.8% after a follow-up period up to 27.5 years. The cancer risk in women with VIN was significantly higher in women with LS compared to women without LS (i.e.

10-years cumulative incidence of VSCC 36.7% in women with LS compared to 8.3% in women without LS, $p < 0.001$) . Subgroup analyses in women with VIN tested for HPV showed that women with HPV positive VIN had a significant lower cancer risk than those who had HPV negative VIN (10-years cumulative incidence of VSCC 9.0% in the HPV positive group compared to 30.4% in the HPV negative group, $p = 0.012$). The cancer risk in women with VIN increased with age ($p < 0.001$).

References

Our findings on a large cohort of women with VIN with long-term follow up support the different routes in vulvar carcinogenesis, with a favourable course in women with HPV-related and LS independent VIN. Because of the increased cancer risk in women with VIN diagnosed at a higher age and in women with HPV negative or LS associated VIN, intensified clinical care is needed in these patient groups.

00444

Why is it important to keep follow-up – a case-report of HPV 16 infection

24. Vulvar diseases and neoplasia

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Background / Objectives

Human papillomavirus (HPV) is the most common sexually transmitted infection. It is well established the relationship between high risk HPV (mostly 16 and 18) and the genesis of cervical cancer. Both primary (vaccine) and secondary prevention (screening with cytology and HPV test) are recommended.

Cervical lesions are the most common but, when the virus is identified, it is important to keep in mind the risk of lesion in other locations.

Results

Case report.

Conclusion

Female, 44 years-old, 1G 1Cesarian. Past medical history: smoker, diabetes mellitus 2 and hypothyroidism. No history of HPV vaccine.

She was referred in 2011 to a gynaecological clinic due to ASC-US result at pap smear. Both colposcopy and vaginoscopy were performed with biopsies: CIN1 and VAIN2. Cervical conization revealed a CIN1.

At the 6 month exam, she had a LSIL cytology, then performing colposcopy with biopsy: CIN 2 and VAIN2. HPV 16 positive.

Kept the follow-up according to Portuguese guidelines, having a NILM cytology, normal colposcopy and negative HPV test for three years.

Four years after the first referral she had a LSIL cytology, HPV 16 positive with normal colposcopy. One year after that, vulvar and vaginal lesions were identified and biopsied - vulvar dysplastic lesion and vagina without dysplasia.

She kept the follow-up at the gynaecological clinic, and seven years after the first appointment (May, 2018) she had a NILM cervical citology, HPV 16 positive and normal colposcopy. Vulvoscopy showed leucoplastic lesions of the posterior third of the large lips, acetowhite lesion with mosaic on the large right lip and on the inner side of the small right lip. Biopsies were performed - VIN 3 usual type (HSIL of the vulva).

A bilateral vulvectomy was performed, with excision of a perineal and a peri-anal lesion (which were not present at the pre-op exam). The anatomopathological examination revealed: High-grade intra-epithelial (condylomatous-u-VIN3) lesion bilaterally on the small and large lips and on the perineum. The peri-anal lesion was a high-grade condylomatous anal intraepithelial lesion (severe dysplasia AIN-3).

The postoperative period had no relevant intercurrences, with favorable healing. The patient remains under surveillance at the gynecology clinic.

References

This case highlights the pathogenesis of the HPV virus (high-risk HPV 16) and host susceptibility, as well as the effects and lesions at levels of the different locations, cervix, vagina, vulva and anus. A correct follow-up allows for diagnosis and treatment of the lesions in earlier stages, however there is an important degree of morbidity associated, which is why primary prevention has a paramount role.

00457

NIPPLE DERMOSCOPY FINDINGS POSSIBLY ASSOCIATED WITH HUMAN PAPILLOMA VIRUS (HPV) AND BREAST CANCER

28. HPV and associated skin diseases

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Background / Objectives

Many breast diseases start on the nipple. Some morbidity that affects the ductal system may show typical lesions on the nipple before clinical detection. In the last twenty years, papers have discussed HPV on the breast cellular cycle, and detected the HPV in breast neoplasia. Recently in the Federal University of Ceara (UFC), the relation between HPV and Breast Cancer (BC) is being studied and HPV DNA was found in 49.5% of patients with BC. Along with other publications on this subject we can infer that HPV can participate in breast carcinogenesis although the cause-effect is not characterized. There is much information about skin and mucosal lesions such as warts, mucosal pigmentation, and vascular alteration mainly in the cervix uteri that are associated to HPV. In January 2018, after authorization by the Ethics Committee of the UFC Hospital we have been researching dermoscopy images to identify findings of HPV on the nipples of patients with BC.

Results

Ten patients after biopsy and diagnosis of ductal carcinoma without clinical signs of nipple-areolar complex infiltration were studied with a dermoscopy guided 2mm punch biopsy followed by Polymerase Chain Reaction (PCR). HPV detection and genotyping were performed through the multiplex nested PCR technique, through a set of primers that amplify the HPV E6/E7 consensus region. HPV genotyping amplified the E6/E7 region of the genome, followed by region-specific amplification for each viral type. Ten types of HPV were investigated: 6/11, 16, 18, 31, 33, 45, 52, 56, and 58. An iPhone 7 adapted with a 10-20x magnification handyscope was used to perform the dermoscopy. The study was approved by the Ethic Committee of Federal University of Ceara

Conclusion

In all patients with breast cancer HPV positive, some nipple findings were observed. The resulting images demonstrate: increased vascularization, micro papillary lesions, small pigmentation changes, white patches and inflammatory lesions, which are frequently associated with HPV in colposcopy findings in HPV induced lesions of the cervix.

References

While some authors have used dermoscopy to identify other diseases on the nipple, such as Paget's Disease and melanomas, none have investigated visually identifiable lesions on the nipple associated with HPV. It is still unknown how HPV reaches the ductal systems, and it is possible that it does so through the nipple. If this is confirmed, a significant step can be made towards identifying a risk of BC. The possibility of a non-invasive method collaborating to the diagnosis of early BC is definitely helpful.

00305

TRENDS IN INCIDENCE, MORTALITY AND SURVIVAL OF PENILE SQUAMOUS CELL CARCINOMA IN NORWAY 1956-2015

36. Public health

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Background / Objectives

To examine trends in incidence, mortality and survival of penile squamous cell carcinoma (SCC) in Norway over 60 years.

Results

Data on all cases of penile cancer diagnosed in Norway during 1956-2015 was obtained from the Cancer Registry of Norway. Trends in age-standardised rates of penile SCC incidence, mortality and 5-year relative survival were assessed by the annual percentage change statistic and joinpoint regression

Conclusion

A total of 1596 penile cancer cases were diagnosed during 1956-2015, among which 1474 (92.4%) were SCC. During 2011-2015, the age-standardised incidence and mortality of penile SCC were 0.91 (95% confidence interval (CI): 0.78;1.05) and 0.50 (0.42;0.60) per 100,000, respectively, and the 5-year relative survival was 61.6% (41.9;76.4). The incidence of SCC increased during 1956-2015, with an average annual percentage change (AAPC) of 0.80% (0.46;1.15). The increase was strongest among men diagnosed at a relatively early age (age<=64 years; AAPC: 1.47% (0.90;2.05)). Mortality also increased over the study period (AAPC: 0.47% (0.10;0.85)), whereas 5-year relative survival did not change (AAPC: 0.08% (-0.19; 0.36)).

References

We conclude that the incidence of penile SCC has increased at a moderate and constant rate during 1956-2015, and that the most consistent increase occurred among younger men. Mortality also increased during the study period. However, survival did not change, thus changes in diagnostics and treatment had little impact

on survival from penile SCC. Since a substantial proportion of penile SCC is caused by human papillomavirus (HPV), the incidence increase may in part be attributed to increased exposure to HPV in the population.

FC 04. Vaccines 1: Male vaccines

00611

HUMAN PAPILLOMAVIRUS (HPV) SEROPREVALENCE AND ANOGENITAL HPV DETECTION AMONG HIV-NEGATIVE MEN WHO HAVE SEX WITH MEN (MSM)

02. Epidemiology and natural history

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Background / Objectives

Although seroprevalence can be used as a crude estimate of cumulative HPV exposure in a population, there are relatively few studies of type-specific HPV seroprevalence in males. We studied HPV seropositivity and anogenital detection at baseline in 602 MSM 17-27 years old participating in a multinational clinical trial of the quadrivalent HPV vaccine.

Results

A highly specific and sensitive competitive luminescence immunoassay (cLIA) was used to measure baseline seropositivity for the HPV types targeted by the 9-valent (9v) vaccine (6/11/16/18/31/33/45/52/58). Intra-anal, scrotal, perineal/perianal, and penile (“anogenital”) swabs were collected at baseline and analyzed for 14 HPV types, including the 9v vaccine types.

Conclusion

At baseline, 228 MSM (38%) had HPV detection of any 9vHPV vaccine type, of whom 41% were seropositive to the same HPV type and 64% were seropositive to any 9vHPV type. Seropositivity concordant with the same HPV type was: HPV6 (56%), HPV11 (35%), HPV16 (36%), HPV18 (23%), HPV31 (27%), HPV33 (11%), HPV45 (11%), HPV52 (17%), HPV58 (20%). HPV type concordance between

anogenital swab and seropositivity varied by swab anatomic location. Intra-anal [46% (38.3-52.7) and peri-anal / perineal swabs [47% (38.3-55.4) had higher concordance among seropositivity and anogenital detection of any of the 9vHPV types as compared to penile [31% (20.8-42.2)] or scrotal swabs [35% (23.5-47.6)]. In a sub-analysis of all 335 trial MSM from the US, EU, and Canada without HPV detection at baseline, 34% were seropositive for any 9vHPV type.

References

Young MSM had evidence of past HPV exposure, even without anogenital HPV detection. Approximately 2/3 of MSM with current anogenital HPV detection were seropositive to any 9vHPV type. HPV exposure in young MSM was common, emphasizing the need to vaccinate prior to sexual debut.

00612

HUMAN PAPILLOMAVIRUS (HPV) SEROPREVALENCE AND ANOGENITAL HPV DETECTION AMONG YOUNG HETEROSEXUAL MEN

02. Epidemiology and natural history

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Background / Objectives

HPV seroprevalence is a marker of cumulative HPV exposure, and though imperfect, can provide a simple measure of HPV exposure in a population. We studied HPV seroprevalence and anogenital detection at baseline in 3,463 heterosexual men (HM) 17-27 years old participating in a multinational clinical trial of the quadrivalent HPV vaccine.

Results

3 extra genital swab (Penile, scrotal, perineal/perianal) samples were collected at baseline and analyzed for 14 HPV types, including types targeted by the 9-valent (9v) HPV vaccine (6/11/16/18/31/33/45/52/58). Seropositivity was measured for the 9v types with a highly specific and sensitive competitive luminescence immunoassay (cLIA).

Conclusion

At baseline, 455 (13%) HM had HPV anogenital detection of at least one 9vHPV type; of these, 13% were seropositive to the same HPV type and 34% were seropositive to any 9v type. Among these 455 men, seropositivity concordant with the same HPV type was: HPV6 (34%), HPV11 (20%), HPV16 (7%), HPV18 (3%), HPV31 (4%), HPV33 (9%), HPV45 (5%), HPV52 (5%), HPV58 (11%). Concordance between anogenital detection at baseline and seropositivity to the same HPV type varied by anatomic location of the swabs. Perianal/perineal swabs had higher concordance between seropositivity and anogenital detection [16.4% (10.7-23.6), overall for any 9vHPV type] as compared to penile [13.0% (9.95-16.7), any 9vHPV

type] and scrotal swabs [11.6% (8.03-16.1), any 9vHPV type]. The older age group of HM (21-27 years old) had overall higher concordance between anogenital detection at baseline and seropositivity to same HPV type [16.4% of 21-27 y.o. vs 10.5% of 16-20 y.o. were seropositive to any 9v type]. In a sub-analysis of a random sample of 208 HM from the US with no HPV detected at baseline, 13% were seropositive to at least one 9vHPV type.

References

Young HM showed evidence of past and current exposure to 9vHPV types. These findings support early age at HPV vaccination in males to maximize vaccine preventive benefit prior to sexual debut.

00500

COMPARISON OF 2-DOSE AND 3-DOSE REGIMENS OF 9-VALENT HPV VACCINE: RESULTS FROM A 3-YEAR RANDOMIZED IMMUNOGENICITY TRIAL

05. HPV prophylactic vaccines

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Background / Objectives

We report 3-year persistence of HPV-antibody responses to the 9-valent HPV (9vHPV) vaccine among girls/boys receiving 2-dose regimens versus girls and young women receiving 3 doses.

Results

In this international, randomized immunogenicity trial (NCT01984697), girls (age 9-14 years) received 2 doses of 9vHPV vaccine (Months 0,6 [n=301] or 0,12 [n=151]) or 3 doses (Months 0,2,6 [n=301]); boys (age 9-14 years) received 2 doses (Months 0,6 [n=301] or 0,12 [n=150]); and women (age 16-26 years) received 3 doses (Months 0,2,6 [n=314]). Anti-HPV geometric mean titers (GMTs) and seropositivity rates were assessed by competitive Luminex immunoassay through Month 36.

Conclusion

Anti-HPV GMTs were highest 1 month after completing the 2-dose or 3-dose series, decreased sharply during the subsequent 6 to 12 months, then decreased more slowly through Month 36. At Months 24 and 36, GMTs in girls and boys given 2-dose regimens were generally similar to or greater than those in women given 3 doses. Month 36 seropositivity rates were ≥83.6% and 81.4% in girls and boys, respectively, vaccinated at Months 0,6; 87.9% among girls/boys vaccinated at Months 0,12; and 91.2% and 77.8% in girls and women, respectively, who received 3 doses.

References

HPV antibody responses persisted through 3 years in girls and boys who received 2 doses of 9vHPV vaccine, with GMTs similar to or greater than those observed in young women receiving 3 doses. Antibody responses generated by 2 doses in girls

and boys may be sufficient to induce high-level protective efficacy through 36 months post-vaccination onset.

00504

LONG-TERM EFFECTIVENESS AND IMMUNOGENICITY OF QUADRIVALENT HPV VACCINE IN YOUNG MEN: 10-YEAR END-OF STUDY ANALYSIS

05. HPV prophylactic vaccines

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Background / Objectives

We report the 10-year, end-of-study analysis of a long-term follow up (LTFU) study that assessed the effectiveness and immunogenicity of the quadrivalent human papillomavirus (qHPV) vaccine in men.

Results

In the 3-year base study (NCT00090285), young men (16-26 years old) were randomized 1:1 to receive 3 doses qHPV vaccine or placebo; results from participants who received 3 vaccine doses and participated in the LTFU are reported. Participants were assessed annually in the 7-year LTFU for HPV6/11-related genital warts and HPV6/11/16/18-related external genital lesions (EGL), and a subpopulation was assessed for HPV6/11/16/18-related anal intraepithelial neoplasia (AIN) or anal cancer. Persistence of anti-HPV6/11/16/18 antibodies was evaluated from serum samples collected 48-72 months (first LTFU visit) and 10 years post-Dose 1.

Conclusion

A total of 917 participants were followed for effectiveness for up to 11.5 years (median: 9.5 years) post-Dose 3. There were no new cases of HPV6/11-related genital warts, HPV6/11/16/18-related EGL, or HPV6/11/16/18-related high-grade AIN during the LTFU in the per-protocol population. One low-grade AIN (AIN1) with positive PCR results for HPV6 and HPV58 was reported. Seropositivity rates based on competitive Luminex immunoassay were >97% at Month 7; remained high over time for HPV6/11/16; and decreased for HPV18 (40.2% at Month 120). Seropositivity

rates at Month 120 assessed by IgG Luminex immunoassay (a more sensitive assay) were>90% for all 4 HPV types.

References

The qHPV vaccine provides durable protection from vaccine-type–related anogenital disease and elicits persistent HPV antibody responses through 10 years post-vaccination onset in 16-26–year-old men.

00583

EFFICACY, IMMUNOGENICITY AND SAFETY OF THE QUADRIVALENT HPV L1 VIRUS-LIKE PARTICLE (VLP) VACCINE IN 16- TO 26-YEAR-OLD JAPANESE MEN

05. HPV prophylactic vaccines

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Background / Objectives

The quadrivalent human papillomavirus L1 VLP (qHPV) vaccine protects against infection and disease related to HPV6/11/16/18. A Phase 3 efficacy, immunogenicity, and safety study of qHPV vaccine was conducted in Japanese men.

Results

In this randomized, double-blind study (NCT01862874), 16–26-year-old Japanese men received 3 doses of qHPV vaccine or placebo (Day 1, Month 2, Month 6). Serum was collected at Month 7 (i.e., 4 weeks post-Dose 3) and Month 36 for analysis of vaccine HPV type antibody responses. Swab samples were collected for analyses of persistent infection. The primary efficacy analysis was performed at an interim analysis; we report end of study results through Month 36. Efficacy and immunogenicity analyses were based on per-protocol populations that included participants who received all 3 vaccinations and were HPV-naïve prior to Day 1 through Month 7 for the relevant type. Vaccine-related serious adverse events (SAEs) were collected throughout the study.

Conclusion

A total of 1124 Japanese men were randomized, 1062 completed the 3-dose vaccination series, and 968 completed the 36-month study. Anti-HPV6/11/16/18 responses in the qHPV vaccine group were markedly induced at Month 7; >97% of participants who received qHPV vaccine seroconverted to each vaccine HPV type at Month 7, and 60.7–92.3% of qHPV vaccine recipients remained seropositive to each HPV type at Month 36. Efficacy of qHPV vaccine against HPV6/11/16/18-related 6-month persistent infection was 85.9% (95% CI: 52.7, 97.3). There were no vaccine-related SAEs or discontinuations due to an adverse event (AE) in the qHPV vaccine group; 3 placebo recipients discontinued due to AEs.

References

The qHPV vaccine was highly immunogenic and efficacious in preventing HPV6/11/16/18/-related persistent infection in Japanese men. The qHPV vaccine was generally well tolerated in this population.

00620

HPV IN MALES: RATIONALE FOR GENDER-NEUTRAL VACCINATION

05. HPV prophylactic vaccines

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Background / Objectives

The incidence of HPV-related disease is high in men and women. Globally, there are >92,000 new cases of oropharyngeal cancer, >48,000 cases of anal cancer and >34,000 cases of penile cancer annually, as well as approximately 32,000,000 cases of genital warts. Effective vaccination programmes are required to reduce the burden. HPV types 6 and 11 are responsible for >90% reported cases of genital warts and recurrent respiratory papillomatosis, and types 16 and 18 for approximately 30% to 90% of reported cases of penile, anal and HPV-associated oropharyngeal and oral cavity cancers. HPV-related cancer incidence is increasing in men. Analysis of a multinational, prospective study evaluating genital, anal and oral HPV natural history, and HPV-related external genital lesions in men (HIM study) reported a higher genital HPV prevalence in men compared with women; furthermore, this prevalence did not vary with age. Oral HPV prevalence is significantly higher in men vs women, and is shown to increase with age in men; incidence is highest at 31 to 50 years of age and lowest at 18 to 30 years of age. In addition, incidence of HPV-related infection of the anal cavity does not vary with age in men. A low rate of seroconversion (at 24 months) following HPV infection is observed in men compared with women. With the exception of HPV type 18, seropositivity is not associated with a lower incidence of HPV infection and, therefore, recurrence of genital HPV infection (high-risk HPV types [16/18/31/33/45/52/58]: 12.8% [incident]; 22.9% [prevalent]) and genital warts is high in men. The data presented herein highlight that men rarely develop immunity following natural HPV infection, regardless of age, and that antibodies acquired from natural HPV infection do not protect against subsequent HPV infection or resultant disease. Men remain susceptible to HPV infection and related diseases throughout the lifespan.

Results

N/A

Conclusion

N/A

References

Adding males to HPV vaccine programmes will result in direct protection against HPV infection, greater and faster disease reductions in females, and add resiliency to national HPV vaccination programmes.

References

N/A

00626

Long-Term Follow-Up Study of Immungenicity and Effectiveness of the 9-Valent HPV (9cHPV) Vaccine in Preadolescents and Adolecsnets (9-15 y.o.)

05. HPV prophylactic vaccines

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00508

A SYSTEMATIC LITERATURE REVIEW OF COST EFFECTIVENESS STUDIES ASSESSING THE NONAVALENT HUMAN PAPILLOMAVIRUS (HPV) VACCINE IN A GENDER NEUTRAL POPULATION

32. Economics and modelling

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Background / Objectives

The nonavalent vaccine protects against nine types of HPV (6/11/16/18/31/33/45/52/58), as opposed to four types with the quadrivalent vaccine (6/11/16/18) and two types with the bivalent vaccine (16/18). Following recommendations from national health authorities, several countries have implemented HPV gender neutral vaccination (GNV) programs. The objective of this systematic literature review was to identify and summarize all available evidence on the cost-effectiveness of national nonavalent HPV vaccination programs in a gender neutral

Results

MEDLINE, EMBASE, Cochrane CENTRAL, EconLit and NHS EED were systematically searched for cost-effectiveness analyses published in the last 10 years in English that met the pre-set eligibility criteria. The Drummond checklist was used to assess the quality of included studies.

Conclusion

Eight studies, based on four model types, were identified from five countries. The main study characteristics and results for nonavalent GNV versus quadrivalent GNV and/or girls' quadrivalent vaccination are presented in Table 1. The incremental cost-effectiveness ratio (ICER) did not exceed the respective local willingness to pay

thresholds in any of the studies reporting these comparisons (n=3). The ICERs were most sensitive to vaccine cost, discount rate and duration of protection parameters although these remained cost-effective. None of the studies included costs related to work productivity loss.

References

Across the five countries with published evidence, HPV GNV with a nonavalent vaccine was cost-effective, cost-saving or dominating compared with a gender neutral quadrivalent vaccination or girls' quadrivalent vaccination. This study supports the continued implementation of HPV vaccination with the nonavalent vaccine on a gender neutral population.

Table 1 Study characteristics and main results

Study	Country	Model type	Vaccine doses	Currency year	Time horizon	Discount rate	Herd immunity?	ICER/QALY 9v GN vs 4v GN	ICER/QALY 9v GN vs 4v girls only
Brisson 2016	United States	Individual based transmission dynamic model†	3	US$ 2010	70 years	3%	Yes	Cost-saving	NR
Simms 2016	Australia	Individual based transmission dynamic model†	2	AUS$ 2013	NR	5%	Yes	NR	Cost-effective, maximal additional cost per dose (9v over 4v): 22.74
Mennini 2017	Italy	Deterministic, dynamic, population based model‡	2	€ 2014	100 years	3%	NR	10,463	13,541
Largeron 2017	Germany	Deterministic, dynamic, population based model‡	2	€ 2014	100 years	3%	No	NR	22,987
Laprise 2016	United States	Individual based transmission dynamic model	2 or 3	US$ 2013	100 years	3%	NR	NR*	NR*
Boiron 2016	United States	Deterministic, dynamic, population based model‡	3	US$ 2015	100 years	3%	NR	16,441	NR
Duhram 2016	Austria	Age structured compartmental model‡	2	€ 2014	2015 to 2050	3%	Yes	Dominates (vs. 2v/4v)	NR
Chesson 2016	United States	Deterministic, dynamic, population based model	3	US$ 2013	100 years	3%	Yes	8,600	NR

2v: bivalent HPV vaccine; 4v: quadrivalent HPV vaccine; 9v: nonavalent HPV vaccine; GNV: gender-neutral vaccination; ICER: incremental cost-effectiveness ratio; NR: not reported; QALY: quality adjusted life-year

† Based on HPV-ADVISE, http://www.marc-brisson.net/HPVadvise-US.pdf

‡ Based on Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. Vaccine. 2010;28(42):6858–6867

* Laprise 2016 compared a 2-dose nonavalent vaccination schedule with no vaccination, and a 3-dose nonavalent vaccination schedule with a 2-dose vaccination schedule. A 2-dose vaccination schedule was shown to be cost-saving compared to no vaccination. A 2-dose vaccination schedule that provides at least 20 years of protection is cost-effective compared to a 3-dose vaccination schedule. However, if a 2-dose vaccination schedule provides less than 20 years of protection while a 3-dose vaccination schedule provides more than 20 years of protection, the 3-dose vaccination schedule yields a substantial increase in QALYs gained.

00501

GENDER-NEUTRAL HPV VACCINATION: FACILITATORS AND BARRIERS TO EXPANDING COVERAGE TO MALES

36. Public health

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Background / Objectives

A greater understanding of the impact of Human Papillomavirus (HPV)–related diseases on males and females has prompted 18 countries to expand their HPV vaccination programs to include both genders. However, broad international support for gender-neutral HPV vaccination (GNV) programs has not been realized. This study aims to capture the experiences and challenges of countries that have implemented GNV programs to share best practices with countries considering similar expansions.

Results

A qualitative study involving in-depth interviews of experts (n= ~18-24) involved in HPV GNV programs in 6 countries (Argentina, Australia, Austria, Brazil, Canada and Italy) is currently underway. The countries were selected based on a literature review of countries with existing GNV programs. Using a semi-structured interview guide, we have obtained insights into countries' decision-making processes for GNV expansion, key strategies and challenges encountered during program implementation, and recommendations for other countries considering expansion. Interviews were audio-recorded and transcribed verbatim in English and/or the local language.

Conclusion

Using a qualitative approach, data from interviews conducted to date were reviewed and coded to identify key themes. Emergent themes encompass factors associated with the selected countries' decision to expand and implement GNV programs. These include the government or health ministry's prioritization of HPV vaccination relative

to other vaccination programs, its role in maintaining and disseminating up-to-date vaccination and disease-related information once a GNV program has been implemented and the role of key stakeholders including media, advocacy groups, and policymakers in supporting GNV programs. To overcome challenges related to these themes, participants made the following recommendations: (1) continuous educational programs for clinicians, school-based providers, and the general population to increase awareness of the HPV-related disease burden, efficacy of the vaccine, and its use in males; (2) utilization of positive outreach to disseminate the benefits of the vaccine to target populations; and (3) implementation of school-based, rather than clinic-based, vaccination programs to increase vaccine uptake.

References

Our initial analysis reveals various factors should be considered when implementing a GNV program, including the education of healthcare providers and support from various stakeholders, including government entities. Moving forward, countries will need to address the gaps between the science and the public's knowledge to effectively and efficiently maintain GNV programs.

FC 05. Epidemiology

00047

AGE-SPECIFIC CERVICAL CANCER INCIDENCE AFTER ELIMINATION OF DIFFERENT VACCINE-PROTECTED HPV TYPES

02. Epidemiology and natural history

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Background / Objectives

By high efficacy of HPV vaccines, several mathematical modelling studies suggest that the elimination of vaccine-protected HPV types is an achievable goal. As different HPV types are associated with invasive cervical cancer (ICC) to a different extent in different age groups, large and comprehensive HPV genotyping series are required for accurate data-driven predictions.

Results

We used the HPV genotyping data (N=2950) that were obtained from the archival tumor blocks of all reported ICC cases in Sweden during a 10-year period (N=4253) in a national study performed by the Swedish National Cervical Screening Registry. We estimated the baseline and the remaining age-specific HPV-related ICC incidences, after eliminating different groups of vaccine-protected HPV types from the population, and the corresponding standardized lifetime risks (SLTR) per 100,000 female births.

Conclusion

The baseline SLTR of HPV-positive ICC was 650 cases per 100,000 female births. After eliminating vaccine types HPV16/18 the SLTR was reduced to 157 for the remaining HPV-positive ICC (24% of HPV-positive SLTR remaining). For the vaccine-targeted and cross-protected types of bivalent, quadrivalent, and nonavalent vaccines, the corresponding remaining SLTRs were 69 (11%), 130 (20%), and 47 (7%), respectively.

References

The predicted population level ICC incidences demonstrate the preventive potential of optimal high-coverage vaccination programs, beyond the vaccine efficacies. The incidences after eliminating all vaccine-protected HPV types are very low, predicting substantial health benefits of effective vaccination programs.

00140

DISTINCT INCREASE IN CERVICAL PRECANCERS IN NORWAY IS EXPLAINED BY BOTH INCREASED EXPOSURE TO HPV AND IMPROVED SCREENING METHODS: NATIONWIDE STUDY FROM 1992 TO 2016

02. Epidemiology and natural history

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Background / Objectives

The aim of this study was to examine the incidence of cervical intraepithelial neoplasia grades 2 and 3 (CIN2, CIN3) and adenocarcinoma in situ (AIS) in Norway during the period from 1992 to 2016 in detail.

Results

From the Cancer Registry of Norway, we identified all incident cases of CIN2, CIN3, AIS and cervical cancers. We used the triannual percentage change statistic for describing alteration in age-specific incidence rates (IR) and age-standardised IRs. The age-period-cohort model was used to distinguish between period and cohort effects. Changes in the coverage of nation-wide screening program and changes in the screening technology used were assessed.

Conclusion

In 2014-2016, women aged 25-29 years of age carried the highest burden of cervical precancers, with the IR of $737/10^5$ for CIN3, $193/10^5$ for CIN2, and $32/10^5$ for AIS. The IR of CIN2 and AIS increased for all age-groups with 20% (95% CI: 2; 43) and with 24% (95% CI: 13; 36) at every 3-years period. From 2011 to 2016, overall 41% increase of CIN3 was observed, whereas the increase was most profound among 25-29-year-old women (62%, 95% CI: 29; 102). Cancer incidence was stable or decreasing. Since 2006, the proportion of screening performed with liquid-based

cytology (LBC) started to increase, escalating in 2010, and in 2016, 86% of all the screening tests performed in Norway were LBC.

References

Some of the observed cohort effects can be attributed to the increased background risks for HPV infection. Age at first sexual intercourse has decreased, while the number of lifetime sexual partners has increased leading to higher exposure to sexually transmitted infections, including HPV. However, a period effect caused by changes in screening and histological verification practices of precancerous lesions may also play the role of the steady increase in incidence over the 25-year study period. For effective control of cervical cancer, treatment of screening-detected cervical precancerous lesions is needed. The observed increase in cervical precancers presents a challenge to assess the effect of cancer prevention programs. Nation-wide registries recording detailed information on screening technology, outcomes and HPV vaccination status will be useful in developing age-appropriate cancer prevention program with minimal overtreatment and related health risks.

00151

HPV type replacement: still too early to tell?

02. Epidemiology and natural history

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Background / Objectives

HPV vaccination has proven effective in reducing transmission and prevalence of the vaccine-targeted and cross-protective types. However, concerns have been raised whether other non-vaccine types (NVT's) will fill the vacated ecological niche. So far, most observational surveillance studies found no evidence for type replacement based on 1) a lower incidence of NVT's among vaccinated compared to unvaccinated individuals in randomized controlled trials; and 2) no significant increase in the prevalence of NVT's within ten years of follow-up compared to the pre-vaccination period. We investigate whether these observations are conclusive for excluding type replacement in the long run.

Results

We studied how the prevalence of a NVT evolves after the introduction of vaccination using an age-structured transmission model with two competing types. We investigated how the timing and strength of type replacement depend on the strength and mechanism of competition, cross-protection and vaccination coverage.

Conclusion

We found scenarios compatible with observations 1) and 2) but yielding type replacement in the long run. Cross-protection may lead to observation 1), although type replacement could occur throughout the population. We identified low coverages under the threshold coverage and competition later in the infection episode to slow down type replacement, so that a follow-up of ten years may fall short. When cross-protection is present but too weak to prevent type replacement, the prevalence of the NVT may even decrease initially before increasing ultimately.

References

Although present evidence is reassuring, trend analyses with longer follow-up are required to rule out type replacement.

00152

EFFECT OF CHANGES TO THE AGE AT FIRST INVITATION TO SCREENING ON MORTALITY FROM CERVICAL CANCER IN ENGLAND

02. Epidemiology and natural history

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Background / Objectives

In 2004 the age of first cervical screening invitation in England was increased from 20 to 25. (1) This reflected evidence that screening at ages 20-24 provided no population benefit in terms of cancer prevention.(2) In 2012, the age of sending out the first screening invitation was changed again; this time to 24.5 years. To enable women to be screened by their 25th birthday.(3)

We previously reported (4) that inviting women at age 25.0yrs was associated with an increase of 43.7 cancers per 100,000 women-years (95%CI: 37.4 to 49.9, $p<0.001$). The increase in the number of cancers diagnosed at age 25 was restricted to cancers stage IA or IB; no increase in advanced (II+) was observed.

Here we aim to explore the effect the age at first screening invitation has had on mortality from cervical cancer.

Results

We have requested data from the national cancer registry in England on number of diagnosis of cervical cancer (ICD10- C53) and estimates by stage of survival at 1, 2, 3, 4 and 5 years after cancer diagnosis.

We have requested that women are grouped (based on year of birth and age at diagnosis) as follows:

1. Aged 20.0-24.5 at diagnosis and diagnosed from 2006 onwards

2. Age 26.0-29.99 at diagnosis and diagnosed 2006 onwards, excluding diagnoses in the first six months of 2009 and the last 4 months of 2008. Also excluding any aged 28 in 2012 onwards.

3. Age 25.0-25.5 at diagnosis in 2009-2016, aged 24.5-25.0 at diagnosis in 2013-2016, Age 25.5-26.0 at diagnosis in 2010-2015.

4. Age 25.0-25.5 at diagnosis in 2006-2008, aged 24.5-25.0 at diagnosis in 2006-2012, Age 25.5-26.0 at diagnosis in 2006-2009.

5. Age 28 at diagnosis in 2012-2016.

Conclusion

We will report KM survival estimates by stage and age at first invitation for screening (as per the groups above). We hypothesis that groups 1, 2 and 4 will all have similar survival (hazard of about 0.9% per year); that the hazard in group 3 would be the lowest (about 0.25% per year) and the hazard in group 5 would be in between (about 0.45% per year). We should have sufficient power to show lower fatality in group 3 compared to group 2.

The following limitations should be considered. We will have no information on when or whether women were invited for screening prior to diagnosis (since these data are not linked to screening data). Not all women will have 5-year follow-up. The analysis is subject to lead-time bias; however, our main interest is to assess whether what we are seeing cancers with lots of lead time or cancers that should have been prevented.

References

Pending

References

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00174

EPIDEMIOLOGY AND CONTROL OF CERVICAL CANCER IN BRAZIL – ROLE OF HPV GENOTYPES

02. Epidemiology and natural history

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Background / Objectives

The estimated age-adjusted incidence of cervical cancer (CC) in Brazil is approximately of 18/100,000 women/year, with large regional differences. Apart from epidemiological interest, recognizing the role of each individual HPV genotype in cervical malignancy became more important after the introduction of HPV vaccines against HPV 16 or 18 infections, showing limited cross protection to other high-risk genotypes non-16/18. Not surprisingly, a new generation of vaccines including another 5 high-risk HPV genotypes have recently been launched. Surveillance with extended genotyping platforms is necessary to identify an eventual emergence of a non-vaccine genotype that may occupy this, to be vacant, ecological niche. However, it is clear that the current vaccines are highly effective on naïve populations but not appropriate to previously and current infected subjects. This translates into the need to screen for CC for the next 50 years. Concerning CC screening, several studies have shown that testing for HPV-DNA is more advantageous than by cytology. Therefore, many countries are remodeling their CC screening program, placing HPV testing as the primary tool and referring to cytology only the HPV+ samples. The objective of this work is to investigate the differential role of HPV genotypes in the epidemiology of cervical cancer in Brazil.

Results

Brazilian studies investigating the distribution of HPV genotypes in the general population and cervical cancer specimens were reviewed and compiled.

Conclusion

Prevalence of high-risk HPVs in Brazil is similar to countries presenting a low incidence of CC, indicating inefficiencies in the national screening program, which relies on cytology. HPV genotyping in large scale has depicted a frequency of HPV genotypes in the general Brazilian female population that is similar to the global

distribution; HPV 16 being the commonest followed by other genotypes according to the study population and geographical region, but not HPV 18. In contrast, on CC cases HPV 18 is the second, being present on 10-15% of all CCs, far after HPV 16 which accounts for 50-70%.

References

Large studies with prolonged follow-up revealed that among HPV genotypes, classified as of high-risk, there are significant differences in their oncogenic potential. Consequently, in the age of personalized medicine, it makes sense to have management strategies according to the genotype or group identified in the sample. Several biomarkers are under evaluation in order to identify on HPV positive cervicovaginal samples, those that present a higher diagnostic or prognostic risk of neoplasia, thus justifying more costly and invasive procedures.

00226

ESTIMATING INCIDENCE RATES OF GROUPED HPV TYPES: A SYSTEMATIC REVIEW AND ANALYSES OF THE IMPACT OF DIFFERENT EPIDEMIOLOGICAL ASSUMPTIONS

02. Epidemiology and natural history

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Background / Objectives

The incidence rate (IR) is an important metric for the occurrence of new cases in a population at risk and is commonly used in studies on HPV. Some studies provide not only type-specific IRs, but also IRs of grouped HPV types, e.g. the IR of all high-risk (HR) HPV types. Researchers take different approaches to calculate such IRs, which may mean that estimates of IRs between studies are not comparable. Here, we assessed the impact of different epidemiological assumptions on the estimated IRs of grouped HPV types.

Results

We first performed a systematic review exploring the approaches used to estimate IRs; papers published from 2010 onwards were included. Subsequently we applied these approaches to data of the H2M study, an observational cohort study of HPV in men who have sex with men. IRs were estimated for six HPV groupings: any HPV, HR-HPV, low-risk (LR) HPV, 2vHPV, 4vHPV, and 9vHPV. We used the midpoint assumption for all analyses, meaning that we assumed an incident event occurred at the midpoint between the last negative and first positive HPV test result.

Conclusion

The systematic review yielded six different approaches (A to F). IRs according to A, B and C, excluded participants who were positive for any of the HPV types of a grouping at baseline, while for approaches D, E and F IRs were estimated regardless of baseline HPV status. Approaches A and D took only the first incident event into account, while approaches B, C, E and F also took subsequent incident events, at later visits, into account. Approaches B and E considered multiple incident events

detected at the same visit as one incident event, while approaches C and F considered each incident event, regardless of timing.

Applying these six approaches to the H2M data (n=749, median follow-up time: 24.2 months), we found large differences in the number of included participants at baseline, the number of incidents events, person-time and the IR. For example, for the HR-HPV group, 356 participants were at risk according to approaches A, B and C, and 749 according to approaches D, E and F; the number of incident events varied between 215 and 975; person-months varied between 5,115 and 17,602; and the IR varied between 3.50 and 5.59 per 100 person-months. The estimated IRs, per HPV grouping, for the six approaches are shown in the figure.

References

In published studies different epidemiological assumptions are used to estimate IRs of grouped HPV types, leading to six different approaches; these approaches lead to widely differing estimates of IRs. Meaning that the interpretation of grouped HPV IRs is not straightforward and that comparison of these IRs between studies is not warranted.

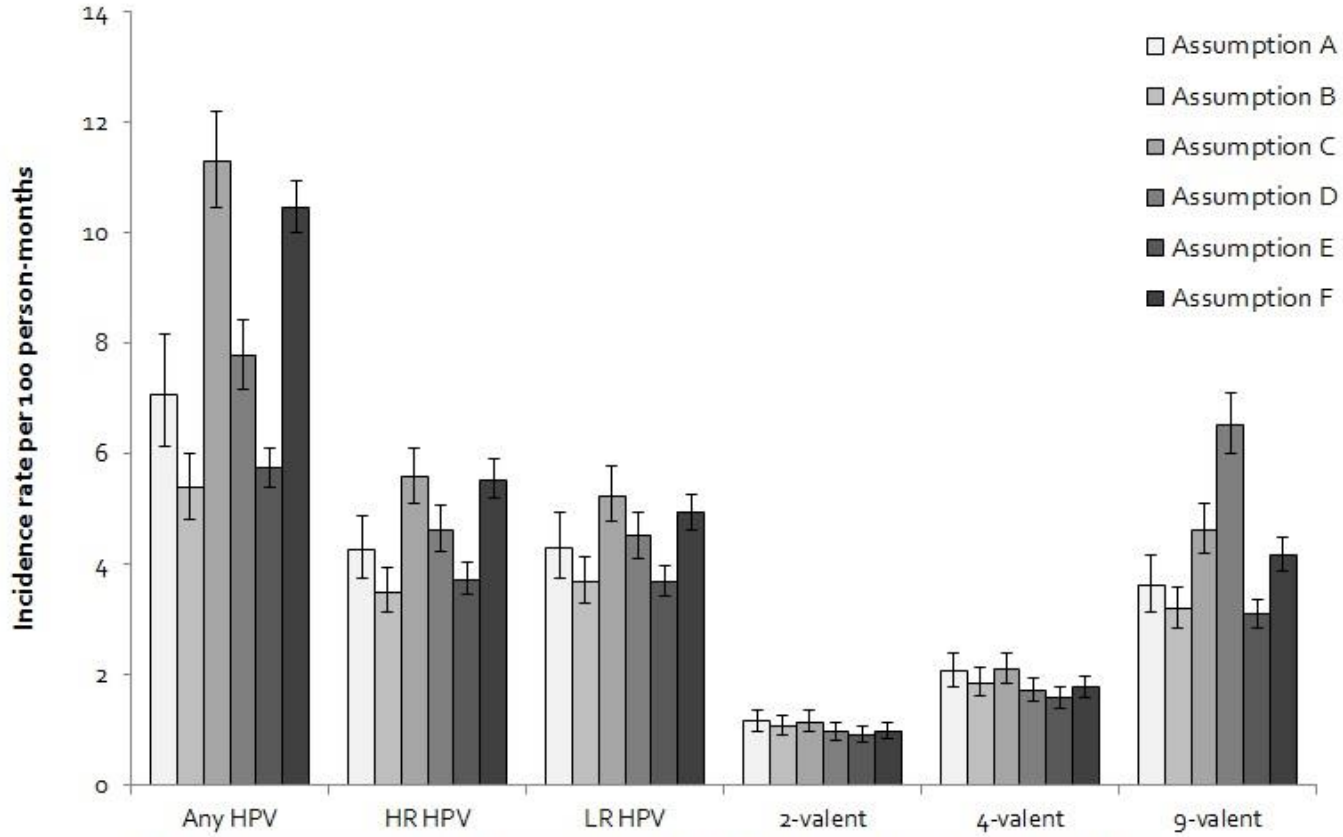

Figure: Incidence rates per 100 person-months of six approaches, shown for six HPV groupings

00410

Prevalence of Vaccine-Targeted High-Risk HPV Types Among Mid-Adult Women in Europe

02. Epidemiology and natural history

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Background / Objectives

Cervical HPV prevalence in the general female population varies by age. We compiled published information on the prevalence of vaccine-targeted high-risk (HR) HPV types in mid-adult women (age 25–45 years) in Europe.

Results

PubMed/EMBASE were systematically searched for original studies, published from January 2013–October 2017, reporting type-specific cervical HPV prevalence among the general population of mid-adult women in Europe. Studies reporting HPV DNA detection of types 16, 18 and ≥1 of 31, 33, 45, 52, or 58 in populations screened for cervical cancer with a mean or median age between 30 and 40 years were included. Key exclusion criteria were age <25 or >45 years only, small study (N<300), not English, and diseased or high-risk population. Data extracted included, type of population, age information, HPV typing and sample collection methodology. Data were pooled on a country- and sub-region level.

Conclusion

Twenty-seven publications were identified: 4 for Eastern Europe (Bulgaria, Czech Republic, Romania; N=4,414 women), 7 for Northern Europe (Denmark, Norway, United Kingdom; N=75,369), 9 for Southern Europe (Croatia, Greece, Italy, Portugal, Serbia, Slovenia, Spain; N=26,136) and 7 for Western Europe (Austria, Belgium, France, Germany; N=8,890). Where reported, vaccination rates were ≤6%. Reported prevalences varied on study and sub-region levels. The pooled prevalence of cervical HPV 16 was 10.8% (range 4.8–17.9% across 4 studies) in Eastern Europe, 5.1% (3.0–6.8%, 7 studies) in Northern Europe, 7.3% (3.7–18.9%, 9 studies) in Southern Europe, and 4.2% (2.1–7.6%, 7 studies) in Western Europe. Pooled prevalence of

HPV 18 was 3.0% (1.8-3.9%, 4 studies) in Eastern, 2.2% (1.1–2.9%, 6 studies) in Northern, 2.1% (1.0–7.8%, 9 studies) in Southern, and 1.0% in Western Europe (0.5–2.1%, 7 studies); prevalence of HPV 31 was 3.5% (1.2–5.0, 4 studies) in Eastern, 3.6% (1.8–4.7%, 5 studies) in Northern, 3.9% (2.0–16.0%, 8 studies) in Southern, and 2.2% (1.2–4.1%, 6 studies) in Western Europe; and prevalence of HPV 52 was 2.7% (1.3–4.0%, 4 studies) in Eastern, 3.8% (1.4–4.9%, 5 studies) in Northern, 2.3% (0.9–6.3%, 8 studies) in Southern, and 1.6% (1.1–3.8%, 6 studies) in Western Europe. Prevalences of HPV types 33, 45 and 58 ranged within 0.9% to 2.5% across sub-regions. Across 3 studies stratifying data by 5-year age sub-groups, HPV prevalences generally decreased with increasing age within the 25–45-year age range.

References

Although estimates vary, HPV 16 is the most common vaccine-targeted HR type in mid-adult European women, followed by 31 and 52 in all regions except Eastern Europe, where type 18 is the third most common type after 31.

00440

Cervical cancer incidence and mortality trends in Latvia in 1993-2016

02. Epidemiology and natural history

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Background / Objectives

Cervical cancer incidence and mortality in Latvia remains among highest in Europe[1,2]. Nationwide organised cervical cancer screening programme was introduced in Latvia in 2009. However, participation rates are unsatisfactory low, below 40% in 2017 [4]. The aim of this study was to examine recent trends in incidence and mortality rates for cervical cancer from 1993 to 2016 by age groups and by the place of residence, and to evaluate the potential impact of the screening program.

Results

The study includes data from the population-based Latvian cancer registry introduced in 1993. The sample includes female patients with diagnosed and histologically confirmed cervical cancer from 1993 to 2016. Data from the Death causes database of Latvia was used for development of the cancer-specific mortality estimates. Age-standardized incidence and mortality rates were calculated by direct standardization method using world standard population. Incidence and mortality changes were detected with joint point regression method using the National Cancer Institute program Joinpoint Software 4.4.0.0 [4].

Conclusion

Age-standardized cervical cancer incidence in Latvia increased from 9.7 to 15.8 per 100 000 females by 2.9% (95% CI: 2.3-3.4%) annually and standardized mortality rose from 4.4 to 5.7 per 100 000 females on average by 1.8% (95% CI: 0.9 -2.8%) annually without any significant changes in trend lines. Most rapid incidence increase was in the age groups 25-39: on average by 4.1% (95% CI: 3.2-5.1) and 40-54: 4.0% annually (95% CI: 3.2-5.1). The greatest increase in cancer-specific mortality was

observed in the age group 40-54: 2.8% average annually (95% CI: 1.4-5.2). The highest incidence rates with the most rapid increase was observed among women living in small towns or rural area: average annual increase by 3.0% (95% CI: 2.3-3.6).

References

Incidence and mortality trends of cervical cancer in Latvia do not show any changes since introduction of the organised population-based screening programme in 2009 and reflects low programme coverage. In developing further activities to improve the coverage women from 25 to 54, as well as those living in small towns and rural area.

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00474

LONG-TERM CERVICAL CANCER RISK FOLLOWING HPV INFECTION – 28 YEAR FOLLOW-UP OF THE MANCHESTER COHORT

02. Epidemiology and natural history

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Background / Objectives

The natural history of HPV infection and subsequent invasive cancer development can only be studied over long periods and in large cohorts. Decisions on implementing primary HPV testing are often based on studies with CIN2 or CIN3 as the primary outcome.

Results

Between 1988 and 1993, in collaboration with over 100 general practitioners and screening clinics in the Greater Manchester area, cervical cell samples were collected from 49,655 women attending for routine cytology screening. There was no age restriction. HPV testing was carried out between 1990 and 1996 on a random sample of 7278 of the women in the cohort, 6462 of whom gave a satisfactory β-globin result. PCR analysis was by HPV L1 MY09/MY11 consensus primers. We have followed the trial cohort to October 2016 through national cancer registration for CIN3 and cancer, giving a median follow-up of 26 years.

Conclusion

47,625 women (96%) were successfully traced. Follow-up identified 1143 cases of CIN3 and 138 invasive cervical cancers. Stored samples from cervical cancers, CIN3s and random controls are being tested for HPV. A preliminary analysis included 126 cases of CIN3 and 17 invasive cervical cancers among 6215 women whose entry sample was tested for HPV in 1990-1996. The cumulative invasive cervical cancer risk 28 years after testing positive for HPV 16/18/39/45 (296 women) was 3.4% (95% CI: 1.8%-6.7%: 9 cancers) and for other HR-types (143 women) was 0.7% (95% CI: 0.1%-5.0%: 1 cancer). The cumulative risk following a negative HPV test (5,776 women) was 0.13% (95% CI: 0.06%-0.28%: 7 cancers). Table 1 shows a

decreasing ratio of CIN3 to invasive cancer with increasing time. CIN3 was rarely diagnosed above age 45. This pattern was also seen among the 439 women testing HRHPV positive.

Table 1: CIN3 and cervical cancer registrations by time since Manchester Study (1988-93) in 49,625 women (upper part) and 6,215 women tested for HPV (lower part)

Time since study	**<5 years**	**5-9.9 years**	**10-14.9 years**	**15-19.9 years**	**20-24.9 years**	**≥25 years**	**Total**
All women (n=47,625)							
CIN3	345	403	256	92	43	4	1143
Cervical cancer	32	28	30	23	21	4	138
CIN3:cancer ratio	10.8	14.4	8.5	4.0	2.0	1.0	
6,215 women HPV tested at entry							
HPV+ (n=439)							
CIN3	32	10	7	0	0	0	49
Cervical cancer	3	3	1	1	1	1	10
HPV- (n=5,776)							
CIN3	21	31	14	8	3	0	77
Cervical cancer	1	1	2	1	2	0	7

References

CIN3 risk declined sharply beyond 5 years after HPV detection, however the invasive cancer risk remains elevated into middle and old age. More detailed results by age and HPV status will be presented.

00054

Socioeconomic factors associated with HPV testing in the National Cancer Data Base

08. HPV testing

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Background / Objectives

HPV-associated oropharyngeal cancers have risen over the last decade to overtake cervical cancer as the most common cancer caused by HPV. Given the increased survival of HPV-associated oropharyngeal cancer and the recent staging changes of HPV-positive oropharyngeal cancer, establishing a baseline rate of HPV testing and determining factors related to HPV testing are exceedingly pertinent.

Results

We used the National Cancer Data Base, accounting for 70% of new cancer diagnoses. About 1500 Commission on Cancer accredited cancer registries submit data to NCDB using standardized data, and coding definitions. To establish a baseline and to reduce heterogeneity in early HPV-testing, we used squamous cell oropharyngeal cancer cases from 2013 to 2015. NCDB requires HPV status reported in the Collaborative Stage Site-Specific Factor 10 for all oropharyngeal cancers. Cases that have a reported HPV status, or have a test ordered but no results were classified as “tested.” If a case is missing HPV status or the record was classified as “test not done,” then cases are classified as “untested.” We used Chi-square test to compare the factors among tested and untested cases. We also calculated odds ratio comparing factors for tested or untested cases with logistic regression.

Conclusion

Overall, 11,195 cases of oropharyngeal cancer fit our inclusion criteria. Of these cases, 65.6% of cases were tested for HPV. Cases with low socioeconomic status are less likely to be tested. About 10% of the non-tested cases are African Americans, while only 7.2% of the tested cases are African Americans. Similarly, 55% of tested cases have private insurance compared to only 41% of untested cases have private insurance. When adjusted in a logistic regression, compared to cases

with private insurance, cases with Medicaid (OR: 0.56; 95% CI: 0.52, 0.61) and uninsured (OR: 0.60; 95% CI: 0.53, 0.67) are less likely to be tested. Cases who live in zip codes with high levels of high school education have 1.42 times the odds (95% CI: 1.30, 1.54) of being tested compared to zip codes in with low. There are also dramatic differences by hospital locations. Hospitals in states located in the West South Central – AR, LA, OK, TX – are far less likely (OR: 0.52; 0.45, 0.60) to test for HPV than the states in New England.

References

The results from this study suggest that cases with low socioeconomic status are less likely to be HPV tested for HPV in NCDB. This heterogeneity in testing is significant given potential de-intensification of treatment for HPV-associated cancer and to maintain equitable treatment for all.

00484

DIFFERENCES IN HIGH-RISK HPV PROFILE ACCORDING TO SEX: RESULTS OF POP-BRAZYL STUDY

09. HPV screening

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Background / Objectives

HPV is a world spread sexually transmitted infection, affecting both genders and implicated in development of different types of cancers as cervical, anal, penile and oropharyngeal. However, the infection rate and types are not equally distributed between genders. Therefore, we aim to describe the high-risk HPV profile according to sex.

Results

We analyzed data from POP-Brazil Study, a cross-sectional nationwide survey who included women and men aged 16 to 25 years. All participants answered an interview with sociodemographic and behavioral questions and provided biological samples for genital HPV analysis after signed an informed consent form. Participants were recruited in primary care unit areas by trained health professionals. We used an automated DNA extraction method (MagNA Pure LC 2.0, Roche Molecular Systems) and HPV genotyping was performed on all specimens using the Roche PCR-based Linear Array Genotyping Test (LA). In all analyses, the data were weighted by population in each capital according to sex within age range of the study. Statistical analysis was performed using SAS software (Statistical Analysis System, SAS Institute Inc., Cary, N.C.), version 9.4, and statistical significance was defined as $p < 0.05$.

Conclusion

We included 5,268 women and 1,119 men with valid samples. The mean age was 21.68 (CI95%, 21.56-21.80) years. The majority of participants self-declared as color brown 56.96% (CI95% 54.77-59.15) and pertained to social class C (55.48%, CI95% 53.32-57.64). The prevalence of high-risk HPV was 35.18% (CI95% 33.13-37.23) with significant differences between genders (38.62% in women and 29.18% in men, p = 0.0002). The high-risk profile was also different, being the most prevalent types 16 (8.92%), 52 (8.84%) and 58 (6.14%) in women, and 59 (6.43%), 51 (5.99%) and 52 (5.96%) in men.

References

Differences in high-risk HPV profile are important and can determine the incidences of HPV driven cancers. These differences must be taken into account in the prescription of HPV vaccines and primary prevention of cancer.

00078

IS EARLY AGE AT THE START OF ORAL CONTRACEPTIVE USE A RISK FACTOR OF CERVICAL ATYPIA?

22. Cervical neoplasia

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Background / Objectives

We investigated whether the risk of cervical atypia (squamous intraepithelial lesions and/or cervical intraepithelial neoplasia) is associated with a short interval between menarche and age at the first sexual intercourse (FSI), and/or between menarche and age at the start of oral contraceptive (OC) use.

Results

A total of 4808 (16-17 years old) Finnish women were enrolled in the PATRICIA trial and received either bivalent human papillomavirus (HPV) 16/18 vaccine or Hepatitis A-virus (HAV) vaccine in 2004-2005. In this study, the association of cervical atypia and interval between menarche and the FSI or age at the start OC use was assessed in the control group (2399) who received HAV vaccination and participated clinical follow-up visits every six months for four years. Altogether 914 women answered the behavioural questionnaire and had a normal baseline cervical cytology test, thereafter performed at semi-annual visits throughout the four-year trial.

Conclusion

The mean age of menarche, FSI and age at first use of OC were 12.4, 16.0 and 16.4 respectively. Among women, who had a shorter than 3 years interval between menarche and the FSI, a very high risk of cervical atypia was associated with concomitant early start of OC use (odds ratio [OR] 5.2; 95% confidence interval [CI], 3.0-9.2). When the start of use of OC was postponed beyond 3 years post menarche it was protective (OR 0.3; 95% CI, 0.2-0.4) although the interval between menarche and FSI remained less than 3 years.

References

Short interval between menarche and age at the start of OC use is a significant risk factor of cervical atypia.

00357

AGE-SPECIFIC HPV GENOTYPE DISTRIBUTION ACCORDING TO CERVICAL HISTOPATHOLOGICAL FINDINGS IN A SCREENED AND UNVACCINATED POPULATION

22. Cervical neoplasia

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Background / Objectives

HPV16 is globally the most common high-risk HPV (hrHPV) genotype and approximately 70% of invasive cervical cancers are associated with HPV16 or 18. Three prophylactic vaccines targeting the highest risk genotypes are commercially available and are in many countries implemented in the national vaccination programmes. Our objective was to study the current age-specific hrHPV genotype distribution in histopathological high-grade cervical lesions in an unvaccinated highly screened population.

Results

The HELICOPTER study (ISRCTN10933736) recruited 1383 women ≥18 years (range 19.2-83.7) attending the single referral colposcopy center in the greater Helsinki area in Finland between 2014 and 2016. Genital samples from 1360 women were tested for 36 HPV genotypes with Luminex assay. Women were divided into three age groups: <30 (n=366), 30-44.9 (n=657), and ≥45 (n=337). Referral reasons and baseline cervical histological findings were recorded, and HPV genotyping results were grouped to mimic the high-risk genotypes covered by the available vaccines: HPV16/18+ (bivalent vaccine), HPV16/18/31/33/35/45+ (bivalent vaccine with cross-protection) and HPV16/18/31/33/45/52/58+ (nonvalent vaccine). The latter two were also analysed excluding HPV16/18. The main outcome measure, histopathological high grade squamous intraepithelial neoplasia or worse (HSIL+) included HSIL, squamous cell carcinoma, adenocarcinoma in situ, and adenocarcinoma.

Conclusion

In total 295 of the 523 cases of HSIL+ (56.4%) were associated with HPV16/18: 64.2% (104/162) in women <30 years, 58.0% (164/283) in women 30-44.9 years, and only 34.6% (27/77) in women ≥45 years of age (p-test for trend 0.002). The bivalent vaccine cross-protection genotypes HPV31/33/35/45 (excluding HPV16/18) on the other hand covered 22.2% (36/162) of HSIL+ in women <30, 23.7% (67/283) in women aged 30-44.9 and increased to 26.9% (21/78) in women ≥45. Correspondingly, in the nonavalent vaccine group HPV31/33/45/52/58 (excluding HPV16/18) accounted for 26.5% (43/162) in women <30 years, 31.1% (88/283) in women 30-44.9 years, and up to 38.5% (30/78) of HSIL+ in women ≥45 years of age. The proportion of HSIL+ associated hrHPV genotypes not included in the vaccines (HPV39/51/56/59/68) also increased with advancing age, from 1.9% (3/162) in <30 years to 7.7% (6/77) in women ≥45 years old.

References

HPV genotype distribution in HSIL+ lesions is distinctly polarised, with HPV16/18 attributed disease markedly more prevalent in young women <30 than among women ≥45 years. This could have implications for the effectiveness of current prophylactic vaccines as well as for current and future screening strategies.

00142

Impact of changes in sexual behavior on past and future trends of HPV infections and related cancers

36. Public health

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Background / Objectives

Changes in sexual behavior are hypothesised to be the main cause of the substantial rise in anal and oropharyngeal cancers in the past two decades in developed countries. Linear extrapolation of current trends have shown that incidence of HPV-positive oropharyngeal cancer could exceed the number of cervical cancers by 2020. However, these projections are not informed by the possible causes of past increases, such as changes in sexual behavior over time. The aim of this study is to understand the potential impact of changes in sexual behavior on past trends of HPV transmission and to predict future trends of HPV-related cancers.

Results

We developed an individual-based model of HPV-transmission using U.S. sexual behavior data from the National Survey of Family Growth, National Health and Social Life Survey, and General Social Survey. These data cover birth cohorts from 1900 to 1999. The model population reproduces the sexual history of annual birth cohorts from 1900 to 1999. We determined, for every modelled individual, the dates of every sexual partnership and with whom it occurred. We performed simulations of HPV-16 transmission, and progression to cancer from 1900 to 2015, taking into account changes in sexual behaviour. We assumed that the probability of transmission per partnership is 100%, the average duration of infection is 1.5 years. We estimated, through model calibration, that the average duration of progression from HPV-16 infection to associated oropharyngeal cancer among men was 43 years. Finally, we assumed that the prevalence of any cofactor of HPV-16 related oropharyngeal cancer (e.g., smoking) has remained stable.

Conclusion

Table 1: Model simulations of HPV-16 prevalence by year of birth

Median prevalence of HPV-16(%)					
	Birth year				
	1900-19	1920-39	1940-59	1960-79	1980-90
Men (15-25 yrs)	3.0	6.6	11.0	13.5	14.6
Women (15-25 yrs)	0.8	2.1	5.6	9.8	11.8

Table 1: Model simulations of HPV-16 related oropharyngeal cancer by year of birth

Median incidence of HPV-16 related oropharyngeal cancer (per 100,000 person-yrs)					
	Birth year				
	1900-19	1920-39	1940-59	1960-79	1980-90
Men					
20-39 yrs	0.0	0.1	0.1	0.2	0.2
40-49 yrs	0.6	1.6	2.7	3.1	3.6
50-65 yrs	2.9	6.7	11.5	13.3	14.1

References

Our results suggest that sexual activity has stabilized for cohorts born after 1960. As a result, the increase in cancer incidence due to sexual activity is predicted to stabilize from 2025 onwards for those younger than 65 years old. Trends in sexual behavior should thus be accounted for when extrapolating HPV-related cancers, or estimating the impact of interventions.

00615

ASSESSING THE RISK OF HUMAN PAPILLOMAVIRUS TRANSMISSION AND HIGH-LEVEL DISINFECTION USING MOLECULAR VIROLOGY APPROACHES

36. Public health

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Background / Objectives

Recent studies have suggested that HPVs are not susceptible to certain high-level disinfection protocols and that medical instruments may provide transmission of nosocomial HPVs infections (1-4). We aimed to determine the infectious load of HPVs from clinical lesions and to investigate HPV virions derived from model systems and clinical lesions in their abilities to be neutralized in classical disinfection protocols.

Results

Infectious HPV virions were isolated from the 293T transfection system, organotypic epithelial tissue cultures, mouse xenografts. Clinical samples from respiratory papillomas and anogenital warts were obtained under IRB approval using emery paper to swab the apical tumors and were typed using the Seegene Anyplex™ HPV28 detection platform. A $TCID_{50}$ assay was validated using RT-qPCR approaches to measure the end-point detection of viral E1^E4 mRNAs in infected HaCaT keratinocytes. A novel focus-forming assay was validated to detect HPV E6/E7 mRNAs as a quantitative, cell-based measure of HPV infetivity. Suspension-based disinfection protocols employed ortho-phthalaldehyde (OPA), hypochlorite and alcohols.

Conclusion

Preliminary assessment of HPV infectious titers suggest that compared to common warts, clinical RRP and anogenital samples have low levels of virions present at apical surfaces. In contrast to other reports, we found HPVs from a variety of sources were susceptible to a 2.5 to 4 $\log_{10}$ reduction in infectious titer when exposed as directed to the disinfectants.

References

We conclude that HPVs are susceptible to a variety of disinfection protocols. We plan to carefully assess the infectious titers of virions present HPV-induced lesions to better determine the risk of transmission from HPV-induced warts.

References

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FC 06. Screening 2: New screening strategies country experiences

00045

PRIMARY HPV DNA SCREENING: TWO YEARS EXPERIENCE AFTER 5Y OF CO-TESTING.

09. HPV screening

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Background / Objectives

To show the effectiveness of Primary HPV testing as a cervical cancer test.

Results

The Hospital of Barbastro serves an area of 107.480 inhabitants, in the North of Spain. Target population is 24,501 women between 30 to 65 years. Patients were attended by midwives in Primary Care Centers and referred to Gynaecological Department when necessary. We screened according to the guidelines of Spanish protocol, SEGO 2010, updated in 2014. PCR hrHPV-DNA test (Cobas 4800®) was used in both periods, which delivers HPV16 and HPV18 genotypes separately and in one group a pool of other 12 hrHPV genotypes. Co-testing was carried out from 2011 to 2015 and Primary HPV testing from 2016 to 2017 with cytology triage. The Pathology Laboratory of the Hospital of Barbastro has accreditation for PAP (conventional and liquid-based cytology) and hrHPV-DNA test (cobas 4800®) according to ISO 15189.

Conclusion

Co-testing and HPV Primary testing were compared: The average number of CIN2+ detected by year was 44.2 cases vs 54.0; the mean age was 37.9±10.2 years vs 38.6±10.2; oncogenic genotypes 16/18 were 59.5% vs 51.4%; microinvasor cases were 38.9% vs 50.0%; coverage was 36.8% to 70.5% in the first period vs 73.9% to 74.4% in the second. Bivariant study showed no statistically significant differences between both periods excepting in the rate of microinvasor cases ($p<0.05$).

Sensitivity for cytology was 79.4 (IC 95%: 71.9-82.9) in the first period and 89.2% (IC 95%: 80.8-94.1) in the second.

References

The increase in the number of cases detected may be due to the coverage increase.

As there are no significant differences in demographic or pathological features between both periods it is suggested that the results of screening are the same.

Primary Care involvement allows screening for cervical cancer to be performed to everybody without additional cost.

Primary HPV testing with partial genotyping is as effective as co-testing and should replace cytology as the first (primary) test in cervical screening.

Quality Assurance in cytological screening is essential to get good results.

00065

HPV AS THE PRIMARY SCREENING TEST FOR CERVICAL CANCER: INITIAL RESULTS FROM A DANISH IMPLEMENTATION STUDY

09. HPV screening

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Background / Objectives

Within the past 10 years, several large randomized trials have shown that a test for human papillomavirus (HPV) is more sensitive than the Pap smear in detecting severe cervical cancer precursor lesions and cancer. Therefore, introduction of HPV-based screening may be very efficient in a Danish setting, as incidence and mortality of cervical cancer is higher than in most other Western European countries.

The objectives of the present study is to compare the clinical performance of human papillomavirus (HPV)-based versus cytology-based cervical cancer screening in a large, population-based implementation study in Denmark.

Results

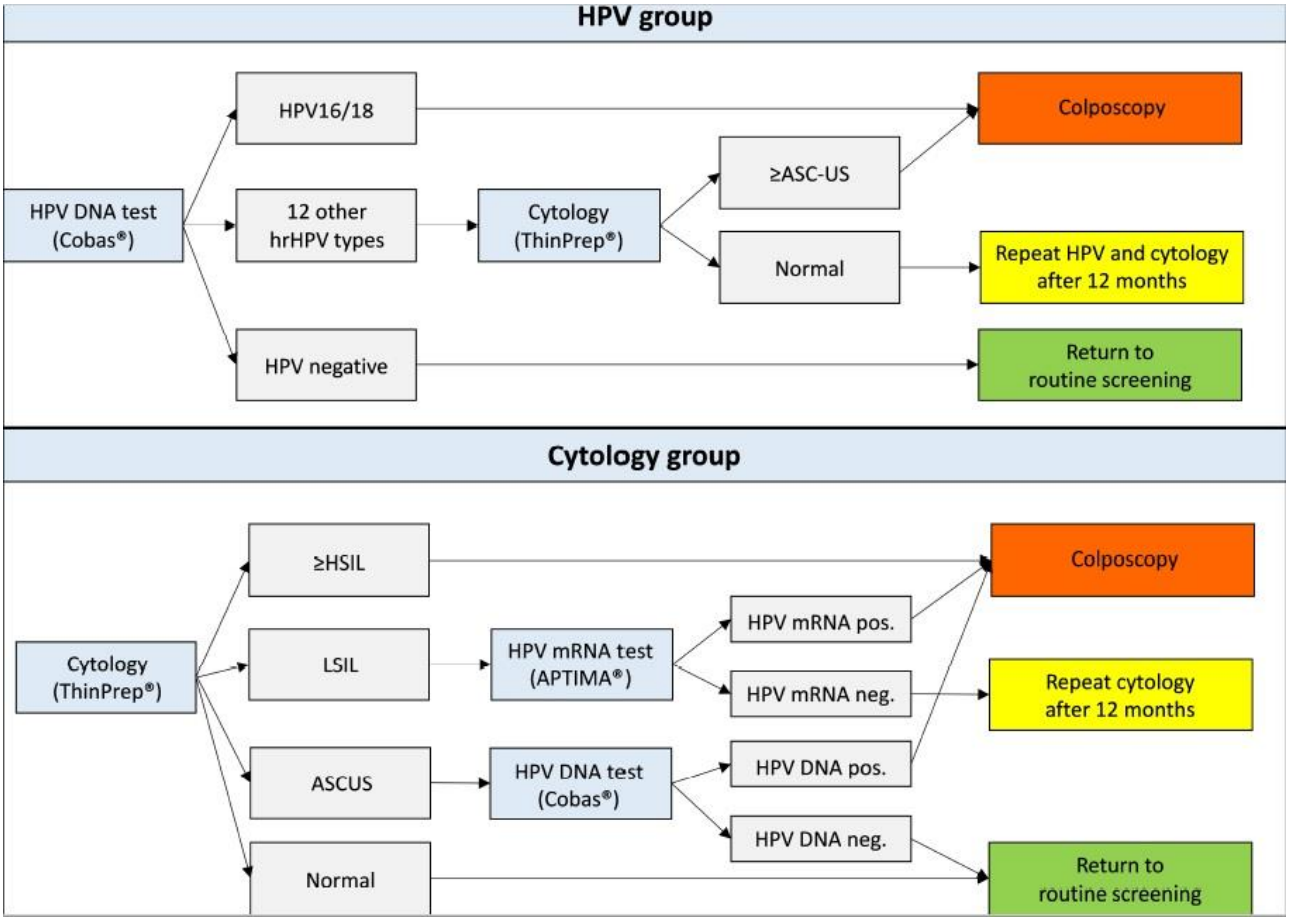
Since May 2017, a pilot implementation of HPV-based cervical cancer screening has been ongoing for women aged 30–59 years in the Region of Southern Denmark. Based on area of residence, women screened in the uptake area of Vejle Hospital are allocated to either HPV-based screening (with HPV16/18 genotyping and cytology triage) or cytology-based screening (with HPV triage for ASC-US/LSIL) (Figure 1). Here, we compare the proportion of unsatisfactory tests and referrals during the first 10 months of implementation.

Conclusion

Until March 2018, 8,851 women were screened by HPV testing and 13,359 by cytology. The age distribution (median [interquartile range]) was similar in the HPV (44 years [37–49]) and cytology (43 years [37–49]) groups. The proportion of unsatisfactory tests was lower in the HPV (0.03%, 95% CI: 0.01%–0.09%) than cytology (0.53%, 95% CI: 0.42–0.67) group. The proportion referred to colposcopy was higher in the HPV (4.0%, 95% CI: 3.6%–4.4%) than cytology (2.2%, 95% CI: 2.0%–2.5%) group. The proportion referred to repeat testing at 12 months was also higher in the HPV (5.0%, 95% CI: 4.5%–5.4%) than cytology (0.2%, 95% CI: 0.1%–0.2%) group.

References

Results for CIN2+ detection will be presented at the conference. HPV-based screening resulted in fewer unsatisfactory tests, but in this initial screening round, more women were referred to colposcopy and repeat testing than with cytology-based screening.



00192

First results of high-risk HPV screening in the cervical cancer screening programme in the Netherlands: participation, referral and detection

09. HPV screening

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Background / Objectives

In January 2017, the Dutch cervical cancer screening programme was changed from a cytomorphological screening to primary high-risk HPV DNA (hrHPV) screening for women between ages 30 and 60. This is the first time in the world, that primary hrHPV screening is nation-wide implemented in the actual population. Women can request a self-sampling set or have a cervical smear taken by their GP. Cytology testing is performed on hrHPV positive samples only. Women with cytological abnormalities (i.e. ASCUS+) are referred for colposcopy and women without

cytological abnormalities have repeat cytology testing after six months. Monitoring of the renewed screening programme is aimed at participation, hrHPV prevalence and the associated referral- and CIN rates.

Results

Screening history data was obtained from the national registry of histo- and cytopathology (PALGA), based on 426,790 primary tests performed in women who were invited in 2017 for the renewed screening programme.

Conclusion

Overall, the hrHPV positive rate was 9.0%, ranging from 21.3% (age 30) to 4.5% (age 60). Cytology was assessed in 98.8% of all hrHPV positives, leading to 32.1% referrals. The CIN2+ detection from colposcopy was 49.7%. 6.9% of the participating women opted for the self-sampling device. At a later stage, we will calculate the total referral and CIN detection rates, including those from follow-up examinations, based on full follow-up data.

References

Primary high-risk HPV DNA screening in the Netherlands leads to the detection of a large proportion of CIN2+ lesions, as a result of a substantial number of referrals for colposcopy.

00193

The longitudinal clinical performance of the RNA-based Aptima Human Papillomavirus (HPV) Assay in comparison to the DNA-based Hybrid Capture 2 HPV Test in 2 consecutive screening rounds with a 6-year interval in a Routine Screening Population of 10.000 women in Germany

09. HPV screening

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Background / Objectives

Longitudinal data on the E6/E7 mRNA-based Aptima® HPV (AHPV) assay exceeding three years in comparison to the gold standard digene Hybrid Capture® 2 (HC2) test are not available.

Results

We previously reported the cross-sectional data of the German Aptima Screening Trial (GAST) where 10,040 women were recruited and tested by liquid-based cytology, the HC2 and the AHPV assay. 411 test-positive women were followed for up to six years. In addition, 3,295 triple-negative women were screened after a median time of six years.

Conclusion

Overall 28 incident CIN3 cases were detected. The absolute risk of developing high risk HPV positive CIN3+ over six years among those women that tested negative at baseline was 2.2 (1.0-4.9) and 2.8 (1.4-5.4) per 1,000 women screened by the HC2 and the AHPV test, respectively (p=0.1094), whereas the absolute risk following a negative LBC test was 9.0 (2.7-30.4). The relative sensitivity of AHPV compared to HC2 was 94.1% for CIN3+ and the negative predictive values were 99.89 (99.77-99.95) and 99.95 (99.83-99.99), respectively.

References

Our data show that the longitudinal performance of the AHPV-test over six years is comparable to the performance of the HC2 test.

00271

HPV FOCAL 48 MONTH EXIT SURVEY: WOMEN'S REAL WORLD EXPERIENCES SURROUNDING PRIMARY HPV TESTING

09. HPV screening

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Background / Objectives

Primary HPV testing for cervical screening has been implemented or being planned in jurisdictions globally. Engaging women who participate in screening prior to implementation is essential to successful transition to HPV testing from Pap screening. HPV FOCAL, a large randomized controlled trial compared primary HPV testing every 4 years to liquid-based cytology (LBC) every 2 years. Women who completed 48mos exit screening were surveyed to assess attitudes and experiences with primary HPV screening.

Results

Women from British Columbia, Canada, aged 25-65 (n=19,009) were randomized to the control (LBC) or intervention (HPV) arms from 2008 to 2012. By 2016, 16,374 women attended exit screening with HPV and LBC co-testing at 48 months. At trial entry, participants were provided information about HPV, cervical cancer, and differences between HPV and Pap testing. In 2017, any women who had completed the 48mos exit screen and had email addresses were invited to complete a survey assessing attitudes to HPV vs. Pap testing, screening intervals, starting age for HPV screening and receipt of HPV positive results. Preliminary summary statistics are presented.

Conclusion

Of the 14,535 invites sent, 5532 (38%) completed some or all of the survey. Of those surveyed, 63% reported having an HPV test to screen for cervical cancer vs. the Pap was acceptable; 54% would be willing to have an HPV test every 4-5 years vs. a Pap every 3 years; and 69% indicated having an HPV test starting at age 30 would be acceptable. When asked about concerns regarding receiving positive results, there were statistically significant differences in distribution of responses between women who ever tested HPV positive (HPV+) vs. women who did not (HPV-); 73% of HPV- vs. 54% HPV+ indicated it would be important for them to know who gave them HPV ($p<0.001$); 25% HPV- vs. 36% HPV+ indicated having HPV would not affect the relationship with their partner ($p<0.001$). However, 70% HPV- vs. 63% HPV+ would feel comfortable telling their partner about the HPV+ result ($p=0.003$) and 36% HPV- vs. 47% HPV+ feel people may judge them negatively for having HPV ($p<0.001$).

References

In a large primary HPV screening RCT, where women were consented and provided with information regarding HPV testing, most women report HPV testing vs. the Pap would be acceptable and just over half would be willing to have HPV testing every 4-5 yrs. Women had varied concerns regarding receipt of HPV positive results. These findings can inform program planning and underscore the need for comprehensive communication and information strategies prior to implementation of primary HPV screening.

00347

Cytological triage and molecular triage with partial genotyping in HPV primary screening: comparison of data from an Italian Region (Tuscany)

09. HPV screening

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Background / Objectives

HPV primary screening requires a triage for positive women and cytology is currently recommended by European guidelines. Some clinically validated HPV tests perform also genotyping and FDA approved a protocol with partial genotyping as triage: all HPV positive women are sent to immediate colposcopy, except for HPV16 and/or HPV18 negative women with normal cytology, who are invited to repeat HPV test and cytology in 1 year.

The objective of the study is to evaluate the performances of partial genotyping as triage, compared to the protocol with cytology.

Results

In Tuscany, a screening validated HPV test that performs a partial genotyping (distinguishing HPV16 and/or HPV18 positive samples from those positive to the 12 “other HPV”) is used. We considered women aged 34-64 years, participating to the HPV primary screening in Florentine area between June 2015-March 2017.

Conclusion

Among 20638 HPV tests executed with partial genotyping, 1529 (7.4%) were positive, of which 452 (29.6%) to HPV16 and/or HPV18.

Cytology triage was abnormal for 418 women (27.3%) and inadequate for 21 (1.4%), with a colposcopy referral rate (RR) of 28.7% (439/1529).

Adhesion to colposcopy was 92.5% (406/439) and 138 (34%) CIN2+ were found.

For 183/452 (40.5%) HPV16 and/or HPV18 positive women, cytology triage was abnormal/inadequate and 80/170 (47.1%) resulted CIN2+.

For 256/1077 (23.8%) “other HPV” positive women, cytology triage was abnormal/inadequate and 58/236 (24.6%) resulted CIN2+.

If we apply the American protocol, the immediate colposcopy RR would be 46.3% (708/1529).

Among the HPV16 and/or HPV18 positive women with normal cytology triage, 56/208 (26.8%) cleared the HPV infection at the 1 year recall and 23/136 (16.9%) CIN2+ were found.

References

Partial genotyping as triage, with sending HPV16 and/or HPV18 positive women to colposcopy, does not result in a change of the immediate colposcopy RR compared to cytology (29.6% vs 28.7%), unlike the American protocol (46.3% vs 28.7%, $p < 0.0001$).

Women with HPV16 and/or HPV18 infection have a greater risk of CIN2+ (47.1% vs 24.7%, $p < 0.002$), but 42% (58/138) of CIN2+ were diagnosed in “other HPV” positive women. So, partial genotyping with sending only HPV16 and/or HPV18 positive women to colposcopy cannot be used as a valid substitute triage method.

Since our protocol does not send HPV16 and/or HPV18 positive women with normal cytology triage to immediate colposcopy, we cannot compare accurately American and our protocols. We can only say that, sending also HPV16 and/or HPV18 positive women with normal cytology triage to 1 year recall instead of immediate colposcopy, we save unnecessary colposcopies for women who clear the infection in 1 year (56/708 = 7.9%).

00370

CANCER CASES IDENTIFIED IN A RANDOMIZED IMPLEMENTATION OF HPV-SCREENING IN THE NORWEGIAN CERVICAL CANCER SCREENING PROGRAMME

09. HPV screening

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Background / Objectives

High risk Human Papilloma Virus (HPV) testing is currently implemented in a randomized controlled fashion as the primary test in the Norwegian cervical cancer screening programme. We present detailed evaluation of the cancer cases identified.

Results

The implementation involves women in the age group 34-69 years in four Norwegian counties, counting approximately 285.000 women. In Norway, the follow-up algorithm after abnormal screening test has been more more aggressive for HPV screening than for cytology screening, referring an increased number of women to direct biopsy, and potentially earlier detection of cancers. Cancer cases, symptomatic and screening detected, are identified for both women allocated to HPV test or cytology. An early concluding cohort, including women who have had time to complete the follow-up algorithm, was used for a more unbiased comparison of the cancer cases. Descriptive analyses of screening results (cytology/HPV status/genotype), screening history, symptoms, FIGO-stadium and age of the cancer-diagnosed women are presented.

Conclusion

By March 2018, approximately 195.0000 women have been screened, half with HPV test and half with cytology. Around 107.000 women have had time to have complete follow-up, and a total of 89 cancer cases are identified in the early concluding cohort; 53 cases belonged to the cohort allocated to HPV testing (40 squamous cell carcinoma, 12 adenocarcinoma, 1 other cervical cancer type) and 36 to the cohort screened by cytology (27 squamous cell carcinoma, 6 adenocarcinoma, 3 other cervical cancer type). Majority of the cancers are diagnosed after the index test

suggested referral to colposcopy and direct biopsy. More than 50% of the women diagnosed with cancer are severe under-screeners/non-screeners. Around 75% of the cancers were related to HPV16 and HPV18, and the majority of the cancers were FIGO stadium I. Updated results will be presented.

References

Most cancer cases identified in the enrolment represent undiscovered premalignant lesions of previous screening rounds, and the actual number of cancer cases should be comparable between the two groups. Our early concluding cohort show a slight increase in the number of diagnosed cancer cases after primary HPV test, and the number of diagnosed cases should be followed closely.

00386

A 5-YEAR FOLLOW-UP STUDY OF THE DIAGNOSTIC EFFICACY USING PRIMARY hrHPV TESTING VS. LIQUIDBASED CYTOLOGY IN CERVICAL CANCER SCREENING OF WOMEN AGED 50+

09. HPV screening

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Background / Objectives

Evidence supports high risk Human Papilloma (hrHPV) testing as the primary screening tool in cervical cancer (CCU) screening. However, many studies on the effectiveness used HC2 HPV DNA as the HPV-test and compare to PAP-smears. Only few evaluated other commercially available tests in comparison with liquid-based cytologies (LBC).

We aimed to evaluate the diagnostic efficacy of hrHPV testing using Cobas® 4800 HPV DNA test (Cobas 4800) as compared to LBC in women aged 50+.

Results

Between September 1st 2011 and September 4th 2012 a consecutive sample of women aged 50+ who were routinely tested for cervical abnormalities in Central Denmark Region were included in the study. The samples were analyzed by both routine microscopy and Cobas 4800. At base-line we calculated the percentage of hrHPV positive test results and percentage of cervical precursors in the LBC. By use of the unique Danish personal identification numbers, all women were followed until December 31st 2017 in the Danish Pathology Register, which contains results of all cervical cytologies and histologies taken in any setting in Denmark. Diagnostic efficacy of LBC and hrHPV-testing was calculated using CIN2+ and CIN3+ lesions diagnosed by colposcopy and biopsy within 5 year as the golden standard.

Conclusion

A total of 4043 women of which 3.93% had ASCUS+ and 8.0% were hrHPV positive at base-line were included in the study. Of these women, 72% were registered with at least one cytology sample or cervical histology in the follow-up period. Sensitivity of CIN2+ was 46.9% (34.3%-59.8%) and 82.8% (71.3%-91.1%) for LBC and hrHPR testing, respectively. The corresponding specificities were 97.0% (96.4%-97.5%) and 93.2% (92.4%-94.0%), respectively. Using CIN3+ as the golden standard the sensitivity was 48.1% (34.0%-62.4%) for LBC and 82.7% (69.7%-91.8%) for hrHPV, while the corresponding specificities were 96.9% (96.9%-97.4%) and 93.0% (92.1%-93.7%), respectively. Two CCU diagnosed at follow-up were overlooked by each of the diagnostic procedures.

References

In this Danish population of women aged 50+ we found a much better sensitivity for CIN2+ and CIN3+ using hrHPV-testing as compared to LBC while specificity decreased slightly. Attention should be paid to the cancer outcomes.

00398

Risks of CIN3+ by cytology and human papilloma virus genotype: A risk-based approach to cervical cancer screening in Norway

09. HPV screening

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Background / Objectives

Primary human papillomavirus (HPV)-based cervical cancer screening was randomly implemented among Norwegian women aged 34 to 69 years in 2015. As an expected consequence of the more sensitive HPV test, there was an increase in the number of positive primary and follow-up tests, decreasing the overall positive predictive value in the follow-up algorithm. Risk stratification of HPV-positive women by HPV genotype may identify women who should be sent immediately to colposcopy/biopsy and those who can be safely followed-up with less invasive testing. The aim of this study was to evaluate the risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) among HPV-positive women, stratified by high-risk HPV genotypes (HPV16/18 vs. other high-risk (oHR)) and cytology diagnosis.

Results

Relevant information on cervical cancer screening and cervical preinvasive lesions and cancer for 94 590 women 34 to 69 years old in the HPV screening arm were extracted from four Norwegian counties from the Cancer Registry of Norway databases.

We estimated the total cumulative risk (CR) of CIN3+ among all HPV-positive women as well as for different combinations of reflex cytology results based on the current triage management of HPV-positive women. As women with atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) potentially represent the group of women most likely to yield a false-positive colposcopy (and benefit from genotyping), we also examined CIN3+ risk among this group of women.

Conclusion

We identified a total of 3059 women aged 34 to 69 years that were HPV-positive. Among this group of women, the overall cumulative risk for CIN3+ was 22.1%. For women with an ASCUS or LSIL reflex cytology result, HPV 16/18-positivity yielded a two-fold higher cumulative risk of CIN3+ compared to women with oHR-positivity (31.8% vs 15.6%, respectively). We also found that women with an HPV16/18-positive infection with NILM reflex cytology yielded a similar cumulative risk as women with an oHR infection with ASCUS reflex cytology result (i.e., 18.4% for HPV16/NILM and 17.3% for HPV18/NILM vs 15.3% for oHR/ASCUS).

References

Follow-up algorithms based on HPV16/18 positivity in women aged 34 to 69 years resulted in better discrimination of those at risk for CIN3+ development. The revised management guidelines by the Norwegian Cervical Cancer Screening Program will recommend clinical actions based on risk, rather than test-based algorithms.

00412

16/18 GENOTYPING OF PERSISTENT HR-HPV INFECTIONS WITH NEGATIVE CYTOLOGY: RESULTS FROM THE ENGLISH CERVICAL SCREENING PILOT

09. HPV screening

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Background / Objectives

In the English pilot of primary cervical screening with high risk human papillomavirus (HR-HPV) testing, HR-HPV positive women were managed as shown in Figure 1. Tests that report HPV 16/18 infections, as well as other HR-HPV infections, were used in three laboratories. This has allowed us to test whether a faster referral of women with HPV 16/18 infections and negative cytology persisting for 12 months would improve clinical outcomes such as detection of high grade cervical intraepithelial neoplasia (CIN 2+) and loss to follow-up, while keeping in balance the number of colposcopies. We compared these genotyping-based outcomes with those from the non-genotyping protocol in which a colposcopy for all women with persistent HR-HPV infections and negative cytology (HR-HPV+/cyt-) was delayed until a 24-month early recall (Figure 1).

Results

We included all 127,238 women aged 24-64 years who had been screened in the three HPV 16/18 reporting laboratories during the prevalence round before 2015. These women had at least 29 months of follow-up in the available data. For each triage protocol, we calculated the numbers of detected CIN 2+, colposcopies, and HR-HPV+/cyt- women not attending the two early recalls in the entire screened population. For the non-genotyping protocol, we estimated the 24-month outcomes for HPV 16/18 infections using attendance, persistence and detection data observed in comparable women in the pilot. The 95% CI were calculated using a parametric bootstrap.

Conclusion

With the genotyping protocol, 2869 CIN 2+ were detected as a result of 8750 colposcopies, and 2378 out of 10,810 HR-HPV+/cyt- women did not attend their early recalls. In the same 127,238 screened women, these numbers would be 2378, 8260, and 2626, respectively, with the non-genotyping protocol. Hence, the genotyping protocol increased the total number of detected CIN 2+ by 1.2% (95% CI: 0.9-1.5) and the number of colposcopies by 5.9% (95% CI: 5.0-6.9) compared with the non-genotyping protocol, and decreased the proportion of HR-HPV+/cyt- women not completing the recommended early recalls by 2.3% (95% CI: -2.5 - -2.1). These numbers were very similar across all age groups, and were robust to varying the assumptions on attendance, persistence and detection at 24 months in HPV 16/18 positive women.

References

Faster referral of HPV 16/18+/cyt- women 12 months after primary screening does not appear to improve to a meaningful extent the clinical outcomes in the English routine cervical screening programme. If anything, more rapid referral of persistently HPV 16/18+/cyt- women increased the number of colposcopies disproportionately relative to the gain in increased detection of CIN 2+, and had little effect on the completeness of follow-up.

Figure 1. Management of women in the English pilot of primary cervical screening with HR-HPV testing.

<table>
<tr><th>Time of testing</th><th>Genotyping triage protocol
(laboratories A, B, C)</th><th>Non-genotyping triage protocol
(laboratories, D, E, F)</th></tr>
<tr><td>Baseline test</td><td colspan="2">HR-HPV negative: routine recall at 3/5 years
HR-HPV positive/positive cytology: colposcopy
HR-HPV positive/negative cytology: early recall at 12 months</td></tr>
<tr><td rowspan="2">Early recall at 12 months</td><td colspan="2">HR-HPV negative: routine recall at 3/5 years
HR-HPV positive/cytology positive: colposcopy</td></tr>
<tr><td>HPV 16/18 positive/cytology negative: colposcopy
Other HR-HPV positive/cytology negative: early recall at 24 months</td><td>HR-HPV positive/cytology negative: early recall at 24 months</td></tr>
<tr><td>Early recall at 24 months</td><td colspan="2">HR-HPV negative: routine recall at 3/5 years
HR-HPV positive: colposcopy</td></tr>
</table>

00058

FIVE-YEAR RISK OF CERVICAL PRECANCER FOLLOWING P16/KI-67 DUAL STAIN TRIAGE OF HPV-POSITIVE WOMEN

13. Screening methods

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Background / Objectives

Human papillomavirus (HPV)-based screening requires triage to avoid unnecessary colposcopy referral while maintaining high sensitivity for cervical precancer. Triage with p16/Ki-67 dual stain (DS) has shown high sensitivity and specificity for detection of cervical precancers; however, prospective studies evaluating the long-term risk of cervical precancer following p16/Ki-67 testing are lacking. Such studies are critical to determine how long a negative DS result indicates a low risk of precancer in order to establish optimal screening intervals. We evaluated the longitudinal performance of p16/Ki-67 DS triage for detection of cervical precancer in a clinical population of over 1,500 HPV-positive women with up to 5 years of follow-up in the context of clinical management thresholds.

Results

1,549 HPV-positive women undergoing screening with HPV/cytology (SurePath) co-testing were enrolled in 2012 at Kaiser Permanente Northern California. Histological endpoints were ascertained from the clinical database through 2017. We estimated 5-year cumulative risks of cervical intraepithelial neoplasia grades 2 or worse (CIN2+) or grades 3 or worse (CIN3+) by baseline p16/Ki-67 DS and cytology at yearly intervals using Logistic Weibull models. Risks were compared to clinical management thresholds for colposcopy referral and a one-year return interval.

Conclusion

p16/Ki-67 DS-positivity predicted significantly higher cumulative 5-year risks of CIN2+ compared to abnormal cytology ($p<0.05$). p16/Ki-67 DS-negative women had

significantly lower 5-year risks of CIN2+ compared to women with normal cytology ($p<0.05$). Similar results were observed for CIN3+. In p16/Ki-67 DS-negative women, the risks of both CIN2+ and CIN3+ remained below the colposcopy referral threshold for all 5 years, and crossed the one-year return threshold at 3 years.

References

Triage with p16/Ki-67 dual stain provides better long-term risk stratification compared with cytology over 5 years. The low risk of cervical precancer in women testing p16/Ki-67 DS-negative permits safe extension of follow-up intervals for 3 years.

00329

DEVELOPMENT OF EVIDENCE-BASED GUIDELINES FOR FOLLOW UP OF WOMEN TREATED FOR CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 OR 3 (CIN2/3) IN ITALIAN SCREENING PROGRAMS.

13. Screening methods

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Background / Objectives

The Italian National Guidelines System of the National Health Institute adopted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology for the development of guidelines. The Italian Group for Cervical Cancer Screening (GISCi) promoted the update of recommendations for post CIN2/3 treatment follow up.

Results

A multidisciplinary panel including all the professionals involved in cervical cancer screening programme and CIN treatment was set up. The GRADEpro online tool was used for: defining and prioritizing clinical questions framed in PICO (Population Intervention Comparator Outcomes); defining and scoring outcomes as critical, important or not important; synthetizing results of the systematic reviews in Evidence to Decision tables and to grade recommendations as strong, conditional (in favour or against) and conditional either the two. Recommendations for six PICOs were published in 2018 (www.gisci.it) while systematic reviews for remaining PICOs are starting.

Conclusion

Sixteen questions were included in the scope and framed in PICOs: 3 about the test to be used (Pap, HPV-DNA or Pap+HPV co-testing or co-testing+colposcopy); 1 about the number of follow up episodes before returning to screening; 6 about the timing of episodes; 3 about the use of diagnostic leep in women with positive follow up test and negative colposcopy; 1 about use of typing test to distinguish persistent

from new infections; 1 about HPV vaccination in treated women. The panel recommended HPV test or co-testing (conditional), but not Pap as follow up test (strong). Colposcopy can be added, but only for assessment of surgical outcomes (conditional either yes or not). Two episodes instead of one, before referring women to regular screening, should be preferred (conditional), because even if some observational studies showed a risk comparable to the general population after one negative co-testing, other studies gave different results. The first episode should be after 6 months (vs. 12) after treatment (strong), in order to avoid progression of undiagnosed prevalent invasive cancers; the interval between first and second episode could be either 6 or 12 months (conditional).

References

Defining evidence based follow up protocols is challenging since no experimental evidence comparing different options is available. Clinical questions should be framed to allow the use of indirect evidence from natural history of the disease and observational studies. GRADE offered a framework to evaluate indirect evidence particularly in accuracy of diagnostics even if dichotomous questions are not the most efficient frame to answer question about frequency and intervals.

00333

SENSITIVITY AND POSITIVE PREDICTIVE VALUE OF HPV E6/E7 mRNA OVEREXPRESSION ASSAY AS TRIAGE TEST FOR HPV POSITIVE WOMEN.

13. Screening methods

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Background / Objectives

Screening by HPV-DNA test showed to be more effective than Pap test in preventing cervical cancer, but the large proportion of women who test positive makes necessary a triage test to refer women to colposcopy.

New Technology in Cervical Cancer 2 (NTCC2) is a randomized trial testing biomarkers for triaging HPV positive women; here we compare accuracy of cytology and an E6/E7 mRNA overexpression assay targeting 14 types (16/18/31/33/35/39/45/51/52/56/58/59/66/68).

Results

More than 41,000 women were recruited in 5 Italian centres (Florence, Veneto, Umbria, Turin, Trento); data from the first 3 centres are included in these analyses. Women were tested with HPV DNA test). Those positive were triaged with cytology and tested for E6/E7 mRNA and other biomarkers. Women with positive cytology were referred to colposcopy, those with negative cytology were randomised to immediate colposcopy or to 1 year HPV re-testing. Women will be followed up until the next screening round (at least for 5 years). All women were tested for E6/E7 mRNA overexpression at baseline. Here we report sensitivity for CIN2+ (at recruitment or at 1 year follow up) of cytology (at ASCUS+ threshold) and of E6/E7 mRNA assay, the rate of positivity, and the estimated positive predictive value (PPV) at baseline.

Conclusion

33,388 women aged 25-64 years have been recruited and 2354 (7.1%) were HPV-DNA positive. 2333 cases have both mRNA and cytology results; 1617 (69%) were positive for mRNA and 651 (28%) for cytology. Cumulatively, 125 CIN2+ (63 CIN2 and 62 CIN3) were found; sensitivity was 96% (120/125; 95%CI 91-99) and 69% (86/125; 95%CI 60-77) for mRNA and cytology, respectively; the estimated PPV was 10% for mRNA (120/1215; 95%CI 8-12) and 15% for cytology (86/581; 95%CI 12-18).

Among the 788 HPV-positive/cytology-negative women randomized to immediate colposcopy, 22 CIN2+ (14 CIN2 and 8 CIN3) were detected (2.8%), while among the 894 randomized to 1 year HPV re-testing, 754 completed the follow up and 17 CIN2+ (10 CIN2 and 7 CIN3) were found (2.3%)(RR 0.81;95% CI 0.43-1.52). The 5 mRNA-negative CIN2+ were found after immediate colposcopy; 2 (1 CIN2 and 1 CIN3) were cytology positive and 3 (all CIN2) were cytology negative.

References

E6/E7 mRNA assay would refer to immediate colposcopy more than 2/3 of HPV-DNA-positive women, but its sensitivity is very high and could allow longer interval for retesting. Similar detection of CIN2+ after immediate colposcopy and 1-year HPV re-testing suggests limited regression, if any, of CIN2+ in one year but current confidence intervals don’t allow excluding a relevant one. Quick regression of mRNA negative CIN2+ could explain the lack of mRNA negative CIN2+ observed in the re-testing arm if confirmed on larger scale.

00037

SCREENING OUTCOME AFTER HPV-VACCINATION IN DENMARK

22. Cervical neoplasia

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Background / Objectives

In Denmark, free HPV-childhood vaccination was offered first to girls born in 1993. In 2016, these girls turned 23 years old and were invited for the first time to cervical screening. The purpose of the study was to determine the effect of this population-based HPV-vaccination.

Results

We followed the closed cohort of women born in 1993, and present in Denmark both when offered HPV-vaccination in 2008 and when invited to screening for the first time in 2016. For comparison we followed a similarly closed cohort of women born in 1983, and present in Denmark when invited to screening for the first time in 2006. Outcome of first screen was determined by linkage to the Danish National Pathology Register. We calculated Relative Risk (RR) and 95% Confidence Intervals (95% CI) for 1) cytology being atypical squamous cells of undertermined significance (ASCUS); ASCUS+; or high grade squamous intraepithelial lesion (HSIL); and for histology being cervical intraepithelial noeplasia (CIN); or CIN3.

Conclusion

In both cohorts, around 60% of women had been screened; around 60% had completed high school; the average age of sexual debut was 16 years; but percent daily smokers at age 15 had decreased from 21% for women born in 1983 to 10% for women born in 1993. In the closed 1993 cohort, 92% of women had received at least one dose of the HPV-vaccine before invitation to screening, while this was 0% for the closed 1983 cohort. For cytology, RR of ASCUS+ was 1.04 (95% CI 0.96-1.12), reflecting the combination of a statistically significant decrease in HSIL; RR 0.60 (95% CI 0.5-0.7) and an increase in ASCUS; RR 1.4 (95% CI 1.2-1.6). In Denmark, women with HSIL are referred directly for colposcopy with biopsy, while women with ASCUS are referred for repeated cytology testing in 6 months. We are currently

analysing these follow-up data, which require a longer observation period that the first screen cytology data.

References

Women in the HPV-vccinated cohort had 40% less HSIL than women in the non-vaccinated cohort. These women are spared referral to colposcopy with biopsy. The observed increase in ASCUS in the vaccinated as compared with the non-vaccinated cohort can probably be explained by the change over time from predominantly conventional to entirely, and mostly SurePath, liquid-based cytology. As we compared entire birth cohorts of vaccinated and non-vaccinated women, our study was free from the selection bias which normally affects comparisons between participants and non-participants in HPV-vaccination. The final answer to the effectiveness of the population-based HPV-vaccination in Denmark will come from the histology data we are currently analysing.

References

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00094

CURRENT STATUS OF CERVICAL CANCER SCREENING PROGRAMS AND HPV VACCINATION IN SOUTHEAST EUROPEAN COUNTRIES

22. Cervical neoplasia

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Background / Objectives

The Southestern Europe HPV Forum is a non-profit and non-governmental organization of southeast European countries established in 2018 with a goal to promote the research of all aspects of human papillomavirus (HPV) infection, to study diseases caused by HPV and help to implement and/or improve primary and secondary prevention programs of cervical cancer and other HPV-related tumours.During the transition period, most of the south-eastern Europe countries experienced significant changes in the healthcare system, especially in the area of medical general practice. Privatization waves have significantly influenced health standards and the availability of health care. Part of the health care has been significantly improved. However, one part of health care has maintained the previous standards or there has been a weakening, especially in the case of diseases and conditions that have a public health significance. Among the world’s leading causes of morbidity and mortality, cervical cancer have understandably been the primary focus of research and development and the dominant motivation for international cooperative efforts at prevention and control.

Results

Successfully organised, population-based cervical cancer screening programmes have not yet been implemented in most southeast European countries despite the greatest burden of cervical cancer. Effective national organized screening in Slovenia

started in 2003, and incidence of cervical cancer decreased since then by 44%. However, the last four years the incidence of cervical cancer recorded the plateau. HPV vaccine coverage in Slovenia is about 55%. In Croatia, the organized cervical cancer screening started in 2012. Through 3 years of program, the incidence of disease was reduced by 18%. Unfortunately, in Croatia HPV vaccination coverage is less than 10% at the state level. In Bulgaria, Romania, Serbia, Montenegro and FYR Macedonia the implementation of organized cervical cancer prevention programmes are in progress, current standard is opportunistic screening with poor coverage. Also, there are no reliable data on HPV vaccination uptake. National-based and country-tailored screening solutions need to be established, using experiences of successful screening programmes in the region.

References

The reframed programs of cervical cancer prevention will include strategic combinations of at least two major components: extension and advancement of existing screening programs using HPV-based technology and implementation of national gender-neutral HPV vaccination in all countries. Understanding the nature of prevention tools, how to use them and how to evaluate their impact is a pressing social demand for the scientific, medical and public health communities.

FC 07. HPV Testing

00009

COMPARISON AND BENEFITS OF FULL GENOTYPING OF ALL 14 ONCOGENIC HPV TYPES USING INNO-LIPA® EXTRA II VERSUS GENOTYPING HPV-16, HPV-18 INDIVIDUALLY AND POOL DETECTION OF 12 OTHER HIGH RISK HPV WITH COBAS 4800® AMONG IRANIAN WOMEN

08. HPV testing

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Background / Objectives

Virtually all Cervical cancers are caused by persistent infection with oncogenic HPV types.HPV 16 and18 Combined are responsible for causing almost 70-75% of all cervical cancers,but the remaining 25-30% of cervical cancers are caused by at least 12 other HR-HPV genotypes;Therfore other oncogenic HR-HPV genotypes demonstrate risk as well for cervical dysplasia and cancer.The aim of this study was to assess whether full genotyping of all 14 oncogenic HR-HPV types are more beneficial.

Results

We examined 1811 women of 25-65 years whom attended DML Medical Center for cervical cancer screening in Mashhad,Iran from June 2017 until July 2018.All participants,before collection of cervical samples,completed a questioner which included their age,Marital status,parity,use of tobacco as well as oral contraceptive pill.All Cervical samples,collected between June to October 2017,were initially tested with cobas 4800 for HR-HPV which detects HPV 16, HPV 18 separately and 12 other HR-HPV types as a group,followed by retesting the samples by INNO-LiPA Extra II which detects 32 HPVs individually;19 HR-HPV as well as 13 LR-HPV types.Both assays were carried out according to manufacturer’s instructions.In the second phase,all positive patients for HR-HPV with Cobas 4800 were asked to return after 9

months from the initial test to assess regression,persistence or replacement of their HPV infection.

Conclusion

From 1811 samples,15.5% (281/1811) were positive for HR-HPV with cobas and 16.8% (305/1811) were positive by INNO-LiPA.WIth Cobas,the most prevalent HR-HPV were HPV-16(28.8%),HPV-18(8.9%),and other HR-HPV(62.2%) and with INNO-LiPA were HPV-16(25.5%),HPV-18(7.5%) and other HR-HPV(66.8%).No major discordant finding were seen between Cobas and INNO-LiPA regarding HPV16 (81 vs. 78) samples and HPV18 (25 vs. 23) samples respectively,however we observed more Positive other HR-HPV by INNO-LiPA(204 vs. 175) since it detects more HR-HPV(19 HR vs.14 HR) per sample.Rescreening positive patients after 9 months,we again detected no discordant finding between Cobas and INNO-LiPA for HPV 16(28 vs. 25), and HPV 18 (8 vs. 6) respectively,but in regard to other HR-HPV,we observed 61 positive HPV by Cobas and 73 positive HPV by INNO-LiPA,but majority of other HR-HPV by INNO-LiPA were replaced by different types since INNO-LiPA detects all other HR-HPVs individually,whereas cobas detects them as a group.

References

This study shows INNO-LiPA Extra II has more advantages since it can fully genotype all 14 HR-HPVs separately and can demonstrate if HPV infection by other HR-HPV types has been replaced, regressed or is still persistent which can help clinicians in clinical follow-up studies of patient, prevention strategies,vaccine efficacy and development of new therapies.

00041

KERATIN-BASED SAMPLE VALIDITY TESTING IMPROVES TRIAGE OF HPV 16/18/45 POSITIVE WOMEN USING hrHPV E7-ONCOPROTEIN TESTING

08. HPV testing

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Background / Objectives

HPV-tests based on the detection of viral oncoproteins are suitable for implementation as a triage method to colposcopy for hrHPV-positive women. The diagnostic capabilities, however, may be limited without assessment of specimen validity to reduce false negative results of these tests. Here we describe the combination of two novel assays: detection of high-risk HPV E7 proteins plus detection of Keratins 5/8/18 from potential basal squamo-columnar junction target cells.

Results

Two sandwich ELISAs – *recom*Well HPV 16/18/45 and *recom*Well Keratin 5/8/18 - were developed for detection of hrHPV E7-oncoproteins and basal keratinocytes. Cervical samples were obtained in PreserveCyte medium from 2637 women who participated in the PIPAVIR studies. All samples were characterized by cytology and HPV-genotyping; E7 and Keratin measurements were performed.

Conclusion

Keratin detection was analyzed and the proportion of invalid samples with results below cutoff was determined. An increase of invalid samples was found in CIN1+ samples (12.4%) in comparison to HPV-negative samples with normal cytology (4.1%).

Sensitivity, specificity, PPV and NPV for *recom*Well HPV 16/18/45 were calculated with HPV 16/18/45 positive samples. An increase in sensitivity of 8.9% was achieved for the CxCa-group when calculated with regard to the results of the *recom*Well Keratin 5/8/18 validity testing. On the contrary, specificity (97.9%/98.0%), PPV (19.5%) and NPV (99.9%) remained constant when compared to the results without validity testing.

	E7 result [included]	**Keratin result [included]**	**E7 result [excluded]**	**Keratin result [excluded]**	**Sens. [Normal Cytology]**	**Sens. [CIN1]**	**Sens. [CIN2]**	**Sens. [CIN3]**	**Sens. [CIS/CxCa]**	**Spec. [CIS/CxCa]**	**PPV [CIS/CxCa]**	**NPV [CIS/CxCa]**
without validity testing	all samples	all samples	-	-	10/120 8.3%	7/45 15.6%	1/28 3.6%	15/31 48.4%	8/10 80.0%	1642/1675 98.0%	8/41 19.5%	1642/1644 99.9%
with validity testing	positive negative positive	positive positive negative	negative	negative	10/116 8.6%	7/37 18.9%	1/25 4.0%	15/29 51.7%	8/9 88.9%	1571/1604 97.9%	8/41 19.5%	1571/1572 99.9%

References

Our results support the detection of hrHPV E7 oncoprotein with *recom*Well HPV 16/18/45 as a method for triage to colposcopy for HPV16/18 positive women in a screening program based on primary HPV screening with HPV16/18 genotyping. Sample validity was analyzed and differences were found in the proportion of valid samples between healthy women and those which developed HPV-induced dysplasia (CIN2+). Validity testing of cervical samples with *recom*Well Keratin 5/8/18 in combination with HPV testing is therefore mandatory to to increase sensitivity for disease with a maximum of specificity, PPV, and NPV.

References

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00074

INTERNATIONAL QUALITY ASSURANCE OF HPV DNA GENOTYPING SERVICES: THE 2017 GLOBAL HPV DNA PROFICIENCY STUDY

08. HPV testing

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Background / Objectives

The International Human Papillomavirus (HPV) Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping. This international HPV DNA genotyping study issued in 2017 assesses the proficiency of the different HPV typing assays used routinely in laboratories worldwide as well as the performance of the laboratory.

Results

Participating laboratories were asked to perform HPV typing using one or more of their usual assays on 41 coded samples composed of purified whole genomic plasmids of sixteen HPV types (HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a and 68b) in a background of human cellular DNA.

Proficient typing requires detection in both single and multiple infections of 50 International Units of HPV 16 and HPV 18 DNA/ 5µl and 500 genome equivalents in 5 µl for the other types, with at least 97% specificity.

Conclusion

The 2017 proficiency study had 115 participating laboratories from all over the world: More than 20 different assays were used to analyse the panel and results from 141 datasets were reported. Participating laboratories were public health laboratories, research laboratories, diagnostic test manufacturers and vaccine companies. We see an improvement in completely proficient laboratories over time from 32% in 2008 to 67% in this year. 70 % of the datasets reported no false negative result in 2017

compared to 43 % in 2008. There is a decrease in not proficient tests with more than 1 false positive result from 36% in 2008 to 14% in 2017.

References

A continuing and increasingly popular global proficiency program promotes comparability and reliability of HPV genotyping assay performance worldwide.

00205

PERFORMANCE OF THE ONCLARITY™, COBAS® AND HYBRID CAPTURE II HPV ASSAYS ON PRESERVCYT® SPECIMENS WITH PANEL-ADJUDICATED HISTOLOGY

08. HPV testing

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Background / Objectives

The BD OnclarityTM HPV Assay U.S. PMA clinical trial enrolled 33,858 subjects and the assay obtained FDA approval in February, 2018 for primary screening, ASC-US reflex, and co-testing claims using BD SurePath™ media (1). A subset of women are being followed in a three year longitudinal study. The trial design includes collection of a Hologic PreservCyt® vial. Residual PreservCyt specimens were stored at -20°C. Here we report the split sample performance of the BD Onclarity, Roche cobas, and Qiagen HC2 using a subset of these archived longitudinal specimens with reference to the panel adjudicated histology results.

Results

A convenience subset of 511 residual PreservCyt specimens were removed from -20°C storage. 161 subjects had a final adjudicated diagnosis of CIN2+, while the remainder, n = 350, had a diagnosis of < CIN2. Samples were aliquoted prior to blinded testing by cobas and HC2 (third party CLIA laboratories running respective FDA-approved tests) or Onclarity (BD Diagnostics), per the manufacturers' instructions. The combined results represent approximately one fourth of the total number of diseased patients in the U.S. PMA trial.

Conclusion

Test	FP	TP	FN	TN	Total*	Sensitivity (95% CI)	Specificity (95% CI)	Positivity (95% CI)
Onclarity	86	93	8	290	477	92.08% (85.14%,95.93%)	77.13% (72.62%, 81.09%)	37.53% (33.3%, 41.95%)
cobas	92	90	11	284	477	89.11% (81.54%, 93.81%)	75.53% (70.94%, 79.6%)	38.16% (33.91%, 42.59%
HC2	92	94	7	284	477	93.07% (86.38%, 96.6%)	75.53% (70.94%, 79.6%)	38.99% (34.72%, 43.44%)

*496/511 patients had valid adjudicated histology results, which included 104 CIN2+ (CIN2 or >=CIN3) and 392 <CIN2 (Negative or CIN1);
477/496 had valid results for all three tests, which included 101 CIN2+ and 376 <CIN2 specimens.

	Sensitivity		Specificity		Positivity	
Test Comparison	**Difference (95% CI)**	**p-value**	**Difference (95% CI)**	**p-value**		**p-value**
Onclarity vs. cobas	2.97% (-5.43%, 11.61%)	0.631	1.6% (-4.49%, 7.68%)	0.668	-0.63% (-6.78%, 5.52%)	0.894
Onclarity vs. HC2	-0.99% (-8.88%, 6.79%)	1	1.6% (-4.49%, 7.68%)	0.668	-1.47% (-7.62%, 4.70%)	0.689

There was no significant difference in clinical performance between assays. All three assays exhibited good sensitivity for CIN2+ disease.

References

The BD Onclarity HPV Assay performed equivalently to two other FDA-approved assays in split sample testing using adjudicated histopathology endpoints.

References

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00229

Buffer and time dependent HPV DNA stability in Colli-Pee® collected FV urine

08. HPV testing

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Background / Objectives

Great interest has been directed towards the use of first-void (FV) urine as a liquid biopsy for high-risk human papillomavirus DNA testing. The positive effect of a conservation buffer on the stability of HPV DNA has been reported previously [(1)]. In this study we examined the impact of different buffer (UCM) conditions and storage time points on the detection of HPV plasmid DNA and human DNA (hDNA) in FV urine samples.

Results

Eight volunteers provided a Colli-Pee® (Novosanis) collected FV urine sample that was aliquoted to test four buffer conditions (no buffer, UCM, fresh UCM) during four different storage time points (72h at room temperature (RT), 7 days RT, 7 days RT + 7 days frozen, 14 days RT). FV urine samples were spiked with HPV16 plasmid DNA and HPV DNA analysis was performed using the Cobas 6800 (Roche). Statistical analysis was performed using JMP Pro 13.

Conclusion

78% (n=25/32) of the FV urine samples without UCM became HPV plasmid DNA negative throughout the different time points. By contrast only 3% (3/93) of the samples with buffer became HPV DNA negative (n=1/3 fresh UCM; n=2/3 UCM), all after 14 days storage at RT. A faster decay of HPV DNA than hDNA was observed. There were no significant differences in HPV DNA in cycle threshold (Ct)-values observed between the buffers used, whereas significant different Ct-values were detected between samples stored for 72h at RT versus (i) 7 days at RT + 7 days frozen at -35°C and (ii) 14 days at RT (Wilcoxon matched pairs signed rank test, $p<0.05$).

References

Significant statistical differences were only observed between samples with buffer and without buffer, no significant differences were observed between the different buffers used. FV urine with UCM appeared to be stable with respect to HPV plasmid DNA for up to 7 days at RT, however after 14 days significant different Ct-values were observed. In addition, hDNA is not an ideal confirmation of good sample storage or processing because HPV DNA seems to decay faster than hDNA, which is in line with previous research.

References

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00238

ONCLARITY PERFORMANCE IN HPV DNA DETECTION OF FORMALIN FIXED PARAFFIN EMBEDDED CERVICAL SAMPLES

08. HPV testing

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Background / Objectives

The causal role of a persistent infection of HPV in cervical pre-neoplastic lesion and carcinoma development has been well established. Diagnosis of HPV infection is usually performed from cervical liquid based cytology specimens (LBC), but these often contain a large amount of HPV genotypes infections, most of which are thought to be transient infections. For this reason, the HPV tests have been developed for cytological samples and clinical cut-off of validated HPV tests is CIN2+ detection. Identification of HPV DNA in cervical tissue could be important for understanding cervical carcinogenesis and for evaluating cervical cancer management. The aim of the study is to evaluate the performance of BD Onclarity HPV test genotyping method on formalin fixed paraffin embedded (FFPE) cervical specimens compared to genotyping results from cytological samples.

Results

: FFPE specimens from women surgically treated for a cervical intraepithelial lesions (CIN) histologically confirmed at the European Institute of Oncology (IEO), Milan, from September 2012 to June 2013 were retrieved from the archives of the Department of Pathology of IEO. A series of 4-µm-thick tissue sections was cut from each paraffin block. The first and last sections were stained with hematoxylin and eosin (H&E) to confirm the histological diagnosis. FFPE and LBC specimens were genotyped using the same extended genotyping Onclarity assay.

Conclusion

Preliminary data on 37 samples (10 CIN1, 12CIN2 and 15 CIN3+) show an overall agreement of 92% for HPV status between FFPE Onclarity samples versus LBC samples. In case of concordance, at least one of the genotypes detected in LBC sample was found in the tissue sample with HPV 16 genotype the most prevalent (41%).

References

Our data demonstrate that there is a very good concordance between HPV genotypes found in cytological and tissue samples, suggesting that the Onclarity method could also be used to detect HPV in tissue samples and that the HPV genotype detected in FFPE samples is one of the HPV detected in cytological samples, supporting the thesis that a lesion is caused by one HPV genotype.

00344

HC2® vs COBAS® 4800: COMPARISON OF CLINICAL AND ANALYTICAL PERFORMANCES OF TWO CLINICALLY VALIDATED TESTS FOR HPV PRIMARY SCREENING OF CERVICAL CANCER

08. HPV testing

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Background / Objectives

In Italy, HPV screening program is started in 2013. In Tuscany Region, it was implemented in women of 34-64 years and two HPV tests, both validated for screening according to European guidelines, were used: HC2® (Qiagen®) until 2016 and Cobas® 4800 (Roche®) from 2016.

The objective is to analyse the impact of the transition from HC2® to Cobas® on HPV screening, comparing clinical and analytical performances.

Results

The study was conducted on two levels:

1) on the same population, comparing screening indicators (of baseline and 1 year recall) before and after passing from one test to another; we considered women participating to the HPV screening program of Florentine area, collected in ThinPrep® (Hologic®) from June 2015 to March 2017;

2) on the same set of samples (HC2® positive retested on Cobas®); the discordant samples were typed on L1 by a Reverse Line Blot method (AB Analitica®) and analysed on a screening assay that targets E6/E7 (BD Onclarity™).

Conclusion

1) On the same population, HPV positivity was 9.8% for HC2® samples and 7.4% for Cobas® ones ($p < 0.0001$). The rates of abnormal/inadequate cytology triage and of adhesion to colposcopy were comparable in the two groups. For women of HC2® group, compared to those of Cobas® group, at immediate colposcopy we found that

the CIN2+ PPV (23.8% vs 34%, p < 0.001) and the rate of normal colposcopies/histologies (44.1% vs 34.2%, p< 0.004) were different with statistical significance. At 1 year recall, all tests were analysed by Cobas® and HPV positivity was respectively 40.7% and 62.2% (p< 0.0001), while CIN2+ PPV was comparable between the two groups.

2) About HC2® positive samples retested on Cobas®, 32.4% resulted HR-HPV negative to the re-test, of which 82.1% had normal cytology. Discordant samples were typed on L1: 7% resulted positive to the 12 HR-HPV and 43.8% HPV negative; 49.2% were positive to HPV types different from the 12 HR-HPV (2/99 CIN3). Among discordant samples resulted negative to the 12 HR-HPV on L1, 14.5% were positive on BD Onclarity™.

References

The use of HC2® as primary screening test, compared to Cobas®, has registered:

- at baseline: greater HPV positivity, similar colposcopy referral rate, lower CIN2+ PPV, higher frequency of normal colposcopies/histologies;

- at 1 year recall (all samples analysed with Cobas®): lower HPV positivity, comparable CIN2+ PPV.

Furthermore, Cobas® is resulted more specific than HC2®: overall, 79.1% of discordant samples resulted HR-HPV negative by typing on L1 or E6/E7. However, the major analytical specificity of Cobas® has determined the non identification of 2 CIN3, detected by HC2® thanks to its cross-hybridization, that thus increases its clinical sensibility.

00352

HPV TYPE-SPECIFIC AGREEMENT BETWEEN LINEAR ARRAY HPV GENOTYPING TEST, ANYPLEX II HPV28 AND 21 HPV GENOARRAY WITHIN THE VALGENT-3 FRAMEWORK

08. HPV testing

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Background / Objectives

To assess human papillomavirus (HPV) type-specific concordance between Linear Array HPV Genotyping Test (Linear Array), Anyplex II HPV28 Detection (Anyplex) and 21 HPV GenoArray Diagnostic Kit (GenoArray) within the third VALGENT study panel (VALGENT-3).

Results

The VALGENT 3 panel comprises samples obtained from women aged 25-64 years attending the national organized cervical screening program in Slovenia (screening population), enriched with 300 cytological abnormal samples (100 ASC-US, 100 LSIL, 100 HSIL). Type-specific agreement for 12 high-risk (hr) HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and 6 low-risk HPV types (HPV6, 11, 42, 53, 66, and 68) common to all three tests were assessed by Cohen’s kappa statistic (κ) and McNemar statistics on a total of 1,600 samples.

Conclusion

Excellent to good agreement between Linear Array, Anyplex and GenoArray was observed for 12 hrHPV types overall and for all individual HPV types, except for HPV42 and HPV68. Whilst Anyplex and GenoArray were in good agreement with each other (κ=0.792 for HPV42 and κ=0.765 for HPV68), they were in fair agreement with Linear Array (κ=0.291 and 0.336 for HPV42 and κ=0.313 and 0.281 for HPV68, respectively). Positivity rate for hrHPV overall and for HPV6, -31, -39, -42, -45, -53, -56, -66, and -68 determined by Anyplex and for hrHPV overall and for HPV31, -42, -45, -51, -56, -59, and -68 determined by GenoArray was statistically significantly higher than that determined by Linear Array (all pMcN<0.05). In addition, positivity rate for HPV42, -51, -53, -59, -66, and -68 was significantly different between

Anyplex and GenoArray. Nevertheless, in the total study population overall agreement between Anyplex, GenoArray and Linear Array was consistently above 96.5% (ranging from 96.5-100.0%) for overall and all individual 18 HPV types assessed.

References

Anyplex, GenoArray and Linear Array showed excellent agreement for the majority of HPV genotypes assessed within VALGENT-3.

00438

Clinical validation of the Liferiver Harmonia HPV assay using the VALGENT-4 framework

08. HPV testing

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Background / Objectives

To evaluate the clinical performance of the Liferiver Harmonia HPV assay (Harmonia) using the international Validation of HPV Genotyping Tests (VALGENT-4) framework.

Results

The VALGENT-4 panel consisted 1,297 samples from women aged 30-59 years who participated in the Danish cervical cancer screening program (998 consecutive samples from routine screening enriched with 299 cytological abnormal samples (100 ASCUS, 100 HSIL and 99 HSIL). Harmonia identifies separately HPV16 and HPV18 and 12 other hrHPV types in aggregate. Disease was defined as histologically confirmed CIN2+ (n= 119 [denominator for sensitivity]), whereas two consecutive negative cytology results were accepted as proxy for non-disease (n=898 [denominator for specificity]). Performance relative to GP5+/6+- PCR-LMNX (standard comparator test) was assessed by a non-inferiority test. Intra/inter-laboratory reproducibility of Harmonia was performed in a subset of 500 randomly selected samples. The benchmarks for acceptable HPV DNA tests in cervical cancer screening are: 0.90, 0.98 and 0.87 for relative sensitivity, relative specificity and inter/intra-reproducibility, respectively.

Conclusion

The relative sensitivity and specificity of Harmonia vs GP5+/6+-PCR-LMNX was 1.06 (95% CI, 1.02-1.11; pn.inf < 0.001) and 0.97 (95% CI, 0.85-0.90; pn.inf = 1.000), respectively. Application of an optimised a-posteriori cut-off for HPV16, HPV18 and other hrHPV types in aggregate led to the relative values of 1.04 (95% CI, 0.99-1.08;

pn.inf < 0.001) and 1.01 (95% CI, 0.99-1.03; pn.inf = 0.002), respectively. The assay showed good intra/inter-laboratory reproducibility (reproducibility ≥ 95%).

References

At the predefined cut-off, Harmonia HPV was statistically more sensitive but less specific than the GP5+/6+-PCR-LMNX for the detection of CIN2+. A posteriori cut off optimization was employed, and when the optimised cut-offs are applied, Harmonia fulfilled international criteria for use in cervical cancer screening.

00462

IS CO-TESTING WITH A 3-TYPE HPV MRNA TEST A BETTER STRATEGY FOR WOMEN 21-29 YEARS THAN CYTOLOGY ALONE?

09. HPV screening

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Background / Objectives

Women in their 20s are advised to get Pap/LBC, not HPV DNA tests because of the high positive rate. The prevalence of CIN3+ within this age group is high. Despite organized cytology screening, cervical cancer incidences are increasing in young women addressing the need of accurate tests. A 3-type HPV mRNA test is more specific than a 14-type HPV DNA test, and may be used in young women. We wanted to estimate the test positive rates and risk of CIN3+ in women 21- 29 years using cytology and a 3-type HPV mRNA E6/E7 test detecting genotypes 16, 18 and 45, the three most prevalent genotypes in cervical cancer.

Results

In 2013-2017, 15,428 women aged 21-29 years attended screening at the University Hospital of North Norway. 9,656 (62.6%) were co-tested using a 3-type HPV E6/E7 mRNA test (PreTect SEE; direct genotyping 16, 18 and 45). The women were followed-up until July 2018. We used histologically confirmed CIN3+ as study endpoint.

Conclusion

During follow-up, we detected CIN3+ in 3.2% (487/15,428) women. The positive rates at baseline for ASC-US+, ASC-H+ and HPV mRNA were 24.8% (3,819/15,428), 5.2% (805/15,428) and 9.7% (935/9,656). For co-testing, the test positive rates were 28.2% (2,725/9,656) and 12.0% (1,160/9,656) with cut-off ASC-US+ and ASC-H+. PPV for CIN3+ for ASC-US+, ASC-H+ and HPV mRNA test were 9.5%, 30.9% and 16.1% PPV for CIN3+ was 19.9% and 40.1% for a double positive co-test using cut-off ASC-US+ and ASC-H+. The risks of CIN3+ were 1.1%,1.6% and 1.4% in cytology negative with cut-off ASC-US+, ASC-H+ and HPV mRNA negative.

The risks of CIN3+ were 0.6% and 0.9% with a negative co-test using cut-off ASC-US+ and cut-off ASC-H+.

References

The 3-type HPV mRNA test has low positive rate and holds high PPV for CIN3+ in women 21-29 years. Co-testing with cut-off ASC-US+ reduced risk for CIN3+ from 1.1% in women with normal cytology to 0.6% in women with a negative co-test. The number of women to be followed up can be reduced from 24.8% using cytology alone (ASC-US+) to 12.0% by using co-test positive with cut-off ASC-H+ without affecting the low risk of CIN3+ in test negative women. Co-testing women in their 20`s with cytology and HPV mRNA improves women’s safety and reduces over referral and overtreatment. By providing clinicians an improved opportunity to address elevated risk, a more accurate patient management can be effectuated.

00111

CLINICAL VALIDATION OF THE COBAS 6800 HPV TEST FOR CERVICAL SCREENING

13. Screening methods

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Background / Objectives

We wished to evaluate the cobas 6800 HPV test in the setting of organized cervical screening, using CIN3+ as the outcome and the cobas 4800 HPV test as the comparator test.
The organized cervical screening program in the Stockholm county, Sweden uses primary HPV screening with the cobas 4800 test and stores all residual ThinPrep liquid based cytology (LBC) cervical samples at minus 25 C after clinical testing.

Results

The samples stored during 2014 and 2015 were linked to the national cervical screening registry to identify all histopathologies taken after the stored LBC sample from these women. We identified stored samples taken <6 months before diagnosis of CIN3+ from 470 women 30-64 years old (the age group targeted by HPV screening in Sweden) and with an HPV test result on file. Controls were matched 2:1 to the case women by birth year and calendar year of sampling and were required to not have a CIN3+ histopathology after the LBC sample, be negative in the HPV screening of the index sample as well as in the cytology screening in the previous screening round. Samples were retrieved from the biobank and tested with both the cobas 4800 and 6800 systems and results were compared to the original 4800 data from the same sample before storage.

Conclusion

Retrieval could be completed for 468 cases and 938 controls. In the original cobas 4800 testing, 466/468 case women were positive. In the 4800 testing of the biobanked samples 462/466 case women were positive and in the 6800 testing of the biobanked samples 462/466 case women were positive.By design, none out of 938

controls were positive in the original cobas 4800 analyses. 3/936 were positive in the 4800 analyses of biobanked samples and 8/933 were positive in the 6800 analyses of biobanked samples. Direct comparison of the 4800 and 6800 in the same archival samples showed a very high concordance (97% of samples with identical results). Variability regarding “invalid” results was found in 9 samples, 7 samples positive in 4800 were negative in 6800 and 12 samples positive in 6800 were negative in 4800.

References

In summary, the cobas 6800 had an overall sensitivity for subsequent histopathology-verified CIN3+ of 99,1%. Compared to the cobas4800 comparator test the relative sensitivity was 100% and the relative specificity was 99,5%.

FC 08. Vaccines 2

00110

LONG-TERM HUMORAL RESPONSE AGAINST NON-VACCINE ONCOGENIC TYPES HPV-31 AND HPV-45 ELICITED BY THE HPV-16/18 VACCINE IN GIRLS AGED 10-14 YEARS: 10-YEAR FOLLOW-UP DATA

05. HPV prophylactic vaccines

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Background / Objectives

Human Papilloma Virus (HPV)-16/18 AS04-adjuvanted vaccine has been shown to induce immune responses against phylogenetically-related non-vaccine types. However the durability of such cross-reactive immune responses is unknown. Here we report the 10-year humoral responses against non-vaccine type HPV-31 and -45 in girls vaccinated with HPV-16/18 AS04-adjuvanted vaccine.

Results

Girls aged 10–14 years who received 3 doses of the HPV-16/18 AS04-adjuvanted vaccine at Month 0, 1, and 6 in the initial observer-blind, randomized, controlled study (NCT00196924) and included in the immunogenicity subset were invited in follow-up studies (NCT00316706 and NCT00877877), with a total follow-up of 10 years after initial vaccination. In this post-hoc analysis, one hundred fifty subjects were randomly selected among the 418 subjects included in the according-to-protocol (ATP) cohort for immunogenicity evaluation of the cross-reactive immune response. Anti-HPV-31 and -45 antibodies were measured in serum samples collected at Month (M) 0, 7, 24, 72 and 120 by enzyme-linked immunosorbent assays (ELISA), using type-specific recombinant virus-like particles as coating antigens.

Seropositivity was defined as antibody titers ≥ 59 ELISA Unit (EU)/mL for anti-HPV-31 and -45.

Conclusion

Among the girls from the ATP cohort who were seronegative for the type analyzed before vaccination and were followed-up up to M120, all had seroconversion to anti-HPV-31 and -45 at M7; at M120, 87.7% and 85.1% remained seropositive for anti-HPV-31 and -45, respectively. The anti-HPV-31 geometric mean titer (GMT) peaked at M7 [2030.5 EU/mL; 95% CI: 1766.2, 2334.4] and decreased to 242.9 EU/mL [95% CI: 201.4, 293.0] at M120. Similarly, the anti-HPV-45 GMT peaked at M7 [2300.8 EU/mL; 95% CI: 2036.8, 2599.0] and decreased to 204.7 EU/mL [95% CI: 170.0, 246.6] at M120.

References

The HPV-16/18 AS04-adjuvanted vaccine, administered at age 10-14 years, induced humoral responses to the non-vaccine types HPV-31 and HPV-45 up to 10 years, supporting the long-term cross-protection observed for the same HPV types.

00216

EPIDEMIOLOGIC IMPACT OF A GENDER-NEUTRAL NONAVALENT HPV VACCINATION PROGRAMME IN COMPARISON TO THE CURRENT GENDER-NEUTRAL QUADRIVALENT HPV VACCINATION PROGRAMME IN SWITZERLAND

05. HPV prophylactic vaccines

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Background / Objectives

An infection with high-risk human papillomavirus (HPV) is the obligatory aetiological factor for the development of cervical cancer. In Switzerland, the prevention strategy for cervical cancer is based on primary prevention via HPV vaccination and secondary prevention with an opportunistic screening programme for precancerous lesions. Vaccination is recommended to 11-26 years old males and females. The objective of the study was to assess the epidemiological impact of switching from the currently implemented programme with the quadrivalent vaccine to the nonavalent vaccine, in an 11-26 years old gender neutral vaccination programme in Switzerland.

Results

A previously validated dynamic transmission model of HPV infections was adapted and calibrated to the Swiss setting assuming an 80% coverage rate in HPV-vaccination and lifelong vaccine type-specific protection. Only cervical disease was taken into account as statistics for other malignant and non-malignant disease caused by HPV were not available in Switzerland. The adaptation was achieved through collection and selection of the most appropriate data to reflect the current Swiss epidemiological and medical context as closely as possible. A gender neutral vaccination programme (males and females) for 11-26 years old with a nonavalent HPV vaccine was compared to the current 11-26 years old gender neutral quadrivalent vaccination programme.

Sensitivity analyses were conducted in order to test the impact of lower vaccination coverage rates and a shorter duration of protection on the model outcomes.

Conclusion

In Switzerland, the nonavalent vaccination programme would result in the additional prevention of 2,983 cervical cancer cases and 28,892 CIN 2/3 cases, compared to the quadrivalent vaccination programme over 100 years. These additional disease cases avoided would correspond to a 24% and 41% cumulative incidence decrease in cervical cancer cases and CIN 2/3 cases, respectively. It would also prevent an additional of 742 cervical cancer-related deaths over 100 years. Results of these analyses are robust since a substantial additional reduction in cervical cancer and precancerous lesions burden is still observed when varying the vaccination coverage rate from 30% to 60% or reducing the duration of protection to 20 years.

References

The switch to the nonavalent vaccine in Switzerland to prevent cervical diseases showed an important contribution in terms of public health impact compared to the quadrivalent vaccine in an 11-26 years old gender-neutral population, even with very conservative assumptions such as low coverage rates or low duration of protection and limiting analysis to only cervical diseases.

00235

OCCURRENCE OF HUMAN PAPILLOMAVIRUS (HPV) TYPE REPLACEMENT BY SEXUAL RISK-TAKING BEHAVIOUR GROUP: POST-HOC ANALYSIS OF A COMMUNITY RANDOMIZED CLINICAL TRIAL

05. HPV prophylactic vaccines

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Background / Objectives

Human papillomavirus (HPV) vaccination programs may cause an increase in non-vaccine HPV types if these eventually take over the vacated ecological niche of the vaccine types. The prerequisites and likelihood of this process known as type replacement probably are different in subpopulations with different risk of acquiring HPV infections. We examined over-time occurrence of non-vaccine HPV types among subgroups with different transmission probabilities up to 8 years post moderate coverage vaccination.

Results

We randomized 33 communities to three arms: Arm A gender-neutral HPV16/18 vaccination, Arm B girls-only HPV16/18 vaccination and hepatitis B-virus (HBV) vaccination of boys, and Arm C gender-neutral HBV vaccination. Out of 1992-94 born resident boys (31,117) and girls (30,139), 8,618 boys and 15,615 girls were vaccinated in 2007-9. Respectively, in 2010-13 8,868 HPV16/18 and non-HPV vaccinated females, and in 2014-16 5,574 initially (2007-9) or cross (2010-13) HPV16/18 vaccinated females attended two follow up visits for cervico-vaginal sampling aged 18.5 and 22 years. The samples were typed for HPV6/11/16/18/31/33/35/39/45/51/56/58/59/66 using PCR followed by MALDI-TOF MS. HPV prevalence ratios (PR) of Arms A/B to Arm C were stratified by *Chlamydia*

trachomatis status, a surrogate of risk taking behaviour. This is an ancillary study to the GSK-sponsored HPV-040 randomized trial (NCT00534638) comparing the overall protective effectiveness of gender neutral and girls-only vaccination strategies.

Conclusion

At the 1st and 2nd follow up visits the PRs in the *C. trachomatis* positives and negatives did not significantly differ for vaccine protected HPV types. Among the initially vaccinated 18.5 year-old females, the HPV52 PR was increased in the *C. trachomatis* positives only (HPV52 PRpos=2.5, PRneg=0.8), but the HPV51 occurrence was consistently somewhat increased (HPV51 PRpos=1.4, PRneg=1.4). In the initially non-HPV vaccinated 18.5 year-old females the HPV51 PR was significantly higher in the *C. trachomatis* positives than in the *C. trachomatis* negatives (HPV51 PRpos=3.8, PRneg=1.2). Among the 22 year-old females, no corresponding significant patterns were observed when comparing the initially HPV16/18 vaccinated to cross-vaccinated but initially non-HPV vaccinated females.

References

The patterns of HPV occurrence post-vaccination may differ in the core group as compared to the general population. However, no consistent over-time indications for type replacement in the vaccinated females were found in either group, although HPV51 merits further follow-up.

00272

HEALTH IMPACT AND COST EFFECTIVENESS OF IMPLEMENTING GENDER-NEUTRAL NONAVALENT VACCINATION IN FLANDERS, BELGIUM

05. HPV prophylactic vaccines

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Background / Objectives

To assess the health impact and cost-effectiveness of gender-neutral HPV vaccination (2 doses, ages 12-13) with a nonavalent HPV vaccine (9vHPV) that protects against the 9 types (6, 11, 16, 18, 31, 33, 45, 52, and 58) responsible for most HPV-related cancers and diseases compared with the current program in Flanders, Belgium, which uses 2-dose bivalent HPV vaccine (2vHPV; HPV16/18) in girls only.

Results

Population-level impact over a 100-year time horizon was simulated in both boys and girls >13 years old using a validated disease transmission dynamic model calibrated to the Flanders region to compare the 2 immunization strategies for prevention of HPV-related cervical cancer (CC); cervical lesions (CIN 2/3, CIN1); vulvar lesions (VaIN); vulvar, vaginal, penile, anal, and head and neck cancers; recurrent respiratory papillomatosis (RRP); and genital warts (GW). Relevant epidemiological, clinical, and cost data were derived from Belgian sources or international literature; GW incidence rates were obtained from a local Belgian study (Dominiak-Felden, 2015). The incremental cost-effectiveness ratio (ICER) was calculated from cost (2017 €) and quality-adjusted life years (QALYs) from this model, at discount rates of 3% and 1.5%, respectively. Deterministic sensitivity analyses were conducted.

Conclusion

Analyses suggest a gender-neutral 9vHPV vaccination program would result in cumulative reductions vs 2vHPV in HPV6/11/16/18/31/33/45/52/58-related-disease

incidence: 18.3% for CC (3,375 cases); 36.9% for CIN2/3 (16,115 cases); 41.2% for CIN1 (11,899 cases); 18.8% and 5.3% (485 and 187 cases) for male and female anal cancer, respectively; 30.1% for penile cancer (514 cases); 85.1% and 85.4% (640 and 808 cases) for male and female RRP, respectively; 84.8% and 85.4% (176,677 and 281,658 cases) for male and female GW, respectively. ICER of implementing 9vHPV gender-neutral vaccination versus 2vHPV vaccination in girls is 5,687€/QALY. Sensitivity analyses show cost effectiveness is maintained with more conservative GW estimates (6,127€ per QALY), when restricted to on-label indications (11,782€/QALY), and versus a quadrivalent HPV vaccine (8,010€/QALY).

References

A gender-neutral nonavalent vaccination program could reduce HPV-related cancers and diseases and be cost-effective compared with the current bivalent program in girls only in Flanders, Belgium.

References

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00275

END OF STUDY RESULTS OF A 2 YEAR MULTICOUNTRY PHASE IV RANDOMIZED COMPARATIVE STUDY OF IMMUNOGENICITY AND SAFETY OF THE AS04-HPV-16/18 VACCINE AND THE HPV-6/11/16/18 VACCINE IN HIV-POSITIVE FEMALE SUBJECTS AGED 15-25 YEARS

05. HPV prophylactic vaccines

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Background / Objectives

Human immunodeficiency virus (HIV) infected subjects are at higher risk of human papillomavirus (HPV) infection. We evaluated the immunogenicity and safety of GSK's AS04-adjuvanted HPV-16/18 vaccine (AS04-HPV-16/18) as compared to Merck's HPV-6/11/16/18 vaccine (4vHPV) when administered to HIV-positive (HIV+) females aged 15-25 years.

Results

In this 2-year, Phase IV, observer-blind, randomized, controlled study (NCT01031069) clinical stage 1 HIV+ subjects and HIV-negative (HIV-) subjects were vaccinated with 3 doses of either vaccine (0, week 6, month 6). Anti-HPV-16/18 antibodies were measured by pseudovirion-based neutralizing assay (PBNA) at Month 0 and 7 and by enzyme-linked immunosorbent assay (ELISA) at all timepoints. HPV-16/18 specific T-cell and B-cell mediated immune responses were assessed by intracellular cytokine assay and enzyme-linked immunospot. Safety outcomes were recorded.

Conclusion

Total vaccinated cohort (TVC) included 257 HIV+ and 289 HIV- subjects. Immunological superiority of the AS04-HPV-16/18 over 4vHPV was demonstrated in HIV+ and in HIV- subjects for HPV-16 and HPV-18 at Month 7 (TVC). At Month 7, in HIV+, anti-HPV-16 and HPV-18 PBNA titers were 2.74 and 7.44 fold higher ($p<0.0001$), respectively, in AS04-HPV-16/18 group compared to 4vHPV group. In HIV-, ratios were 3.05 and 5.38, respectively ($p<0.0001$). Non-inferiority of immune response of AS04-HPV-16/18 in HIV+ over 4vHPV in HIV- was shown in the according to protocol cohort (ATP). At Month 24, antibody concentration by ELISA in the AS04-HPV-16/18 groups remained above those in the corresponding 4vHPV groups for both antigens, and overall, antibody responses appeared lower in HIV+ versus HIV-. Seroconversion rates at Month 24 in HIV+ for HPV-16 were 100% in the AS04-HPV-16/18 and 94.7% in the 4vHPV groups, and were 96.3% and 67.6% for HPV-18, respectively (in HIV-: 100% in all except for HPV-18 in 4vHPV: 98.5%) (ATP). There was a trend for better CD4 and B-cell response with AS04-HPV-16/18 versus 4vHPV. CD4 response was similar in HIV- and HIV+. B-cells response appeared better in HIV- versus HIV+. No safety concerns were raised.

References

In this 15-25 year-old cohort of HIV+ and HIV- women, AS04-HPV-16/18 was shown immunologically superior to 4vHPV. Antibody response remained sustained over 24 months but appeared lower in HIV+ versus HIV- for both vaccines. AS04-HPV-16/18 has the potential to induce a longer-lasting protection against HPV-related lesions and cancers in HIV+ and HIV- compared to 4vHPV.

00374

BIVALENT HPV VACCINE EFFECTIVENESS CORRELATES WITH PHYLOGENETIC DISTANCE TOWARDS VACCINE TYPES 16 AND 18

05. HPV prophylactic vaccines

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Background / Objectives

We previously demonstrated cross-protection against specific oncogenic HPV types among Dutch women aged 16 to 24 years, who had been eligible for vaccination with the AS04-adjuvanted bivalent vaccine (2vHPV) since 2009 and visited sexually transmitted infection clinics in the Netherlands between 2011 and 2015 [1]. To reconcile inconsistencies in cross-protection reported across 2vHPV studies, and to substantiate the presumed type-restricted nature of protection elicited by virus-like particles (VLPs) targeting L1 capsid protein, we re-evaluated vaccine effectiveness (VE) against type-specific HPV positivity as a function of phylogenetic distance.

Results

We recalculated type-specific VE by the logistic mixed model from the original publication [1], for all genotypes in the SPF10-LiPA25 assay. Phylogenetic distance was calculated from reference DNA sequences (including those used for construction of VLPs) obtained via the PapillomaVirus Episteme database [https://pave.niaid.nih.gov/]. We performed a phylogenetic analysis based on L1 amino acid composition, as well as on *L1* capsid gene and whole genome sequences (WGS). We fitted penalized regression splines to VE as a function of minimum distance of each type to L1 VLP in protein analysis, and to HPV-16 or 18 reference sequences in DNA analyses.

Conclusion

Overall, there was a clear relationship between VE and phylogenetic distance to L1 VLP (Spearman's ρ= −0.68, p<0.001). Predictions from the estimated spline function suggest that 2vHPV provides partial cross-protection against HPV-31, 33, 35, 45, 52, and 58, i.e. high-risk types with close phylogenetic relationships to HPV-16 or 18. Cross-protection to low-risk types, including HPV-6 and 11, is not to be expected. Analyses based on *L1* capsid gene (ρ= −0.65, p<0.001) and WGS (ρ= −0.77, p<0.001) yielded comparable results as those for L1 protein. In partial correlation analysis, WGS phylogenetic distance to HPV-16 or 18 was the strongest independent determinant of VE.

References

Our findings indicate that WGS phylogenetic distance to HPV-16 or 18 better explains cross-protection by 2vHPV than distance measures based solely on L1, and suggest that cross-protection induced by 2vHPV primarily extends to the same high-risk types, albeit with moderate efficacy, as included in the nonavalent HPV vaccine.

References

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00476

Systematic literature review of neutralizing antibody immune responses to non-vaccine high-risk HPV types induced by the bivalent and the quadrivalent vaccineses

05. HPV prophylactic vaccines

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Background / Objectives

Partial and inconsistent efficacy against some HPV types not targeted by the bivalent (2v) and quadrivalent (4v) vaccines has been reported. We reviewed the literature on neutralizing antibody immune responses to non-vaccine high-risk HPV types 31, 33, 45, 52 and 58.

Results

PubMed/EMBASE were systematically searched for full-text, original articles, published in English from Feb 2008–Feb 2018, reporting serum antibody responses against non-vaccine HPV types using pseudovirion-based neutralization assays. Studies of healthy subjects receiving 3 vaccine doses were included; immunocompromised populations were excluded. Data extracted included seropositivity (% of subjects with antibody titer above a study-specific threshold) and antibody titers by time from 1st vaccine dose.

Conclusion

Seven publications met inclusion criteria: 3 reported on the 2v vaccine, and 4 (3 RCTs and 1 cohort study) compared the 2 vaccines. Among adolescent girls, seropositivity for HPV 31 at 7–12 months post 1st dose was significantly higher with the 2v than with the 4v vaccine in one (93 vs 56%, P<.05, N=50) but not in another study (97 vs 89%, P>.05, N=188); seropositivity for HPV 45 was higher with the 2v vaccine in both studies (36 vs 6%, P<.0001 and 64 vs 19%, P<.05). Seropositivity with the 2v vs the 4v vaccine was 74 vs 53% for HPV 33, 64 vs 19% for HPV 52 and 39 vs 20% for HPV 58 (N=188). Among young women, one 2v vaccine study (N= 45)

reported 74% seropositivity for HPV 31 and 61% for HPV 45 at 12 months compared to 11% and 13%, respectively, at baseline. However, an RCT (N=27) of young women found that neither of the 2 vaccines induced HPV 45-neutralizing antibodies. Among adult women (18–45 years, N=1106), seropositivity with the 2v versus the 4v vaccine for HPV 31 was 69 vs 40% at month 7, but dropped to 28 vs 29% at month 24; for HPV 45, seropositivity was 24 vs 6% at month 7, dropping to 15 vs 3% at month 24. In contrast, one small 2v vaccine study (N=12) reported that HPV 31 and 45 neutralizing antibody responses were maintained over 36 months. Vaccine-induced HPV 31 and 45 neutralizing antibody titers were generally 2–4 logs lower than titers against their related vaccine-targeted types, 16 and 18.

References

In contrast to neutralizing antibody responses to types covered by HPV vaccines, HPV 31-antibodies are detected within 6 months of the 3rd dose in some but not all females receiving the 2v or 4v vaccines. Seropositivity rates, particularly for HPV 45, are variable, and neutralizing antibody titers significantly lower than titers against vaccine-targeted types. The largest published study suggests limited durability of cross-neutralizing antibodies.

00523

TYPE-SPECIFIC DATA ON HUMAN PAPILLOMAVIRUS INFECTION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA IN THE ASIA-PACIFIC REGION

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

To assess the availability of recent type-specific data on human papillomavirus (HPV) infection in oropharyngeal squamous cell carcinoma (OPSCC) and report type-specific HPV prevalence in OPSCC in the Asia-Pacific region.

Results

PubMed/Medline and EMBASE databases were systematically searched for full publications reporting type-specific HPV DNA detection in histologically confirmed OPSCC. Bibliographies were also searched. Original studies reporting on all of the following were included: overall HPV, types 16 and 18 and ≥1 other high-risk type. Key exclusion criteria were: publication before 2012, not English, special populations (e.g., HIV-infected only) and small study (N<25). Key information, including study type, country, population characteristics, sample type, HPV assay, HPV types detected, p16INK4a expression, and E6/E7 mRNA detection, was extracted.

Conclusion

Fourteen publications reporting on type-specific distribution were included: 13 reported data on OPSCC overall, 5 on tonsillar SCC, 4 on base of tongue SCC, and 2 on other OPSCC sites. Six studies originated from Eastern Asia (China and Japan only), 3 from Southern Asia (India only), 2 from Oceania (Australia and New Zealand), and 1 each from South-Eastern (Singapore), Central (Kazakhstan) and Western Asia (Israel). Across the Asia-Pacific region, HPV DNA was detected in 43.5% of 1,707 OPSCC cases overall, 50.0% of 142 tonsillar SCC, 20.9% of 239 base of tongue SCC, and 5.5% of 55 OPSCC cases from other anatomic sites. HPV

16 was detected in 88.4% of HPV-positive OPSCC, followed by HPV 18 (5.4%), HPV 31 (3.2%), HPV 45 (3.0%) and HPV 33 (1.3%). The prevalence of other HPV types was <1%.

References

Most of the recent data on HPV type-specific distribution in OPSCC in the Asia-Pacific region originates from Eastern Asia. Detection of HPV OPSCC varies across anatomic subsites and is most common in tonsillar SCCs. HPV 16, 18, 31, 45 and 33 are the types that were identified.

FC 09. Anal neoplasia

00278

Anal liquid-based cytology and high risk human papilloma testing as composite endpoint in HIV-infected men who have sex with men to optimize screening for anal neoplasia

09. HPV screening

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Background / Objectives

Screening methods for anal intraepithelial dysplasia (AIN) are suboptimal, require high observer experience and anal cytology has a lower specificity than cervical cytology. This study aimed to determine the diagnostic performance of a composite endpoint comprising anal liquid-based cytology (aLBC) and high-risk human papillomavirus (HR-HPV) testing to predict histological high-grade squamous intraepithelial lesions (hHSIL).

Results

From a cohort of HIV-infected men who have sex with men (MSM) seen at a Spanish University hospital, all patients who had an aLBC with concomitant HR-HPV testing were included. hHSIL were determined by high-resolution anoscopy (HRA)-guided biopsy and included AIN grade II-III.

Conclusion

A total of 705 visits obtained from 426 patients were included. The prevalence of HR-HPV among the different aLBC results were: 51.9% (133/215) normal, 87.9% (20/232) low-grade squamous intraepithelial lesions (LSIL), 13.3% atypical squamous cells of unknown significance and 90.9% (149/164) HSIL; p(linear

association)<0.001. A low prevalence of hHSIL was only observed for the composite aLBC/HR-HPV-testing endpoint “normal/noHR-HPV” (10%) and “LSIL/noHR-HPV” (4%), while 29% of those with normal cytology but HR-HPV showed hHSIL. The prognostic values (95% confidence interval) for HR-HPV to predict hHSIL in normal cytology were: Sensitivity, 83% (69.2%-92.4%); specificity 44.1% (36.4%-51.9%); positive predictive value (PPV), 29.3% (25.6%-33.3%), negative predictive value (NPV), 90.2% (82.8%-94.7%). Corresponding figures for cytologic LSIL were: Sensitivity, 98.8% (93.3%-99.9%); specificity, 17.9% (12.1%-24.9%); PPV, 39.2% (37.4%-41.1%); NPV, 96.4% (78.9%-99.5%). Here, only 4% of those without HR-HPV showed hHSIL. A positive interaction and a synergistic effect for the composite endpoint was observed (relative excess risk=1.50, attributable proportion of histological results to the interaction=0.17, synergy index=1.24). Given the high proportion of hHSIL in those patients with normal aLBC/HR-HPV despite the considerably low VPP, as well as the almost absent prevalence of histological HSIL in those without HR-HPV despite cytological mild dysplasia, it should be considered to modify the widely used recommendations to refer all patients with cytological LSIL to HRA, while sparing HRA in individuals with normal cytology.

References

HRA may be spared in the setting of LSIL/noHR-HPV followed by aLBC-based screening. In contrast, HIV-infected MSM with normal aLBC but HR-HPV infection should be considered for
HRA.

00279

Assessment of the learning curve of high-resolution anoscopy in HIV-infected men who have sex with men: how to improve the performance?

09. HPV screening

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Background / Objectives

High-resolution anoscopy (HRA) with subsequent biopsy to detect high squamous intraepithelial lesions (HSIL) is characterised by a long learning curve. Starting the learning process, especially without supervision, is difficult and based on studying a high number of images and the scarce number of manuals available, as well as revising the results with a specialized pathologist. This study aimed to determine the required learning time and to identify factors that impact on the training process.

Results

From September 2010 until July 2017, all HIV-infected men who have sex with men seen at one consultancy of a tertiary care centre in Spain, were invited to be screened for HSIL by means of HRA with biopsy. In the present study, all those who for the first time underwent HRA with subsequent anal biopsy conducted by one single observer and who had no prior test for anal lesions including digital-rectal examination, HPV testing or anal liquid-based cytology (aLBC), were included.

Conclusion

Eighty-five (14.7%) of the 581 patients included presented histological HSIL. The factors associated with the capacity to detect HSIL in biopsy were the presence of cytological HSIL [adjusted odds ratio (aOR): 3.04, 95%CI: 1.78-5.21; p<0.001], infection with high-risk human papilloma virus (HR-HPV) (aOR: 2.89, 95%CI:1.38-

6.05; p=0.005), the number of biopsies taken per HRA (aOR: 1.28, 95%CI: 1.07-1.52; p=0.006) and tobacco smoking (aOR: 1.75; 95%CI: 1.12-2.73; p=0.014). Two events independently augmented the detection rate of HSIL: first, the moment one single experienced pathologist interpreted biopsies after 409 HRA (aOR: 2.80, 95%CI: 1.74-4.48; p=0.035) and second, the HRA observer underwent an additional training after 536 HRA (aOR: 2.57, 95%CI: 1.07-6.16; p=0.035). The prevalence of histological HSIL was 9.3% until the first event, 22.8% between the two events and 39.1 after the second event. A learning process could be observed throughout the whole study period without an increase of HR-HPV prevalence.

References

The long learning process supports the growing evidence that the proposed training volume of 50-200 performances is underestimated. Extensive training of both anoscopist and pathologist is warranted and the development of tools to support the diagnostic performance may be considered.

00059

LONG-TERM PERFORMANCE OF HPV GENOTYPING, HPV E6/E7 MRNA EXPRESSION, AND P16/KI-67 CYTOLOGY FOR DETECTION OF ANAL PRECANCER IN HIV+ MSM

25. Anal neoplasia

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Background / Objectives

Biomarkers of HPV-related cervical carcinogenesis may have applications for anal cancer screening in high-risk populations such as HIV-positive (HIV+) men who have sex with men (MSM); however, prospective studies are needed to evaluate the long-term reassurance and safety of a negative test result. Here, we evaluated the longitudinal performance of several biomarkers including high-risk (HR) HPV DNA testing, HPV16/18 genotyping, HPV E6/E7 mRNA, and p16/Ki-67 dual stain (DS) in a population of HIV+ MSM.

Results

This study includes 363 HIV+ MSM enrolled at an HIV/AIDS clinic between August 2009 and June 2010 with passive follow-up through October 2015. All men had anal cytology and high-resolution anoscopy (HRA) at baseline; cytology and histology disease endpoints were combined to account for potential misclassification by HRA and biopsy placement. We calculated the sensitivity and specificity of each biomarker for anal intraepithelial neoplasia grade 2 or worse (AIN2+) detection at baseline and at the end of follow-up. For each biomarker, we estimated the cumulative risk of AIN2+ at 2 and 5 years by summing the probability of prevalent disease and incident disease risk calculated from logistic and Cox regression models, respectively.

Conclusion

Among the 363 men included in our study (median age 53 years), 167 had no dysplasia (46%), 92 had AIN1 (25%), 48 had AIN2/HSIL (13%), and 56 had AIN3/HSIL (16%) at baseline. Of 259 with <AIN2 at baseline, a total of 135 (52%) had follow-up (mean = 2.8 years) and 25 developed incident AIN2+ (10 AIN2 and 15 AIN3; mean follow-up time = 2.1 years). HR-HPV testing had the highest positivity and sensitivity, but the lowest specificity of all assays. HPV16/18 genotyping and HPV E6/E7 mRNA both had lower positivity and high specificity for AIN2+ detection, but much lower sensitivity compared with the other assays. The 2-year and 5-year cumulative risks of AIN2+ were highest in men testing positive for HPV16/18 (59.6% and 71.6%) and HPV E6/E7 mRNA (60.3% and 72.7%), followed by DS (52.0% and 63.8%) and cytology (51.6% and 61.4%), respectively. Men testing HR-HPV-negative (3.3% and 7.3%) and DS-negative (7.6% and 9.4%) had the lowest 2-year and 5-year cumulative risks of AIN2+, respectively. The 2-year risks for HR-HPV and DS negatives were lower than the baseline AIN2+ risk in men who were cytology-negative (8.0%).

References

Biomarkers evaluated for cervical cancer screening show long-term risk stratification for AIN2+. Baseline HR-HPV and DS negativity indicate low risk of AIN2+ for at least 2 years compared with anal cytology; however, the high positivity of HR-HPV in this population may limit its utility for surveillance and management of HIV+ MSM.

00105

HOST CELL DNA METHYLATION MARKERS FOR THE DETECTION OF HIGH-GRADE ANAL NEOPLASIA AND ANAL CANCER IN HIV+ MEN WHO HAVE SEX WITH MEN

25. Anal neoplasia

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Background / Objectives

High-grade anal intraepithelial neoplasia (AIN2/3; HGAIN) is highly prevalent in HIV+ men who have sex with men (MSM), but only a minority will eventually progress to cancer. Currently the cancer risk cannot be established, and therefore all HGAIN are treated, resulting in overtreatment. We assessed the potential of host cell DNA methylation markers for detecting HGAIN and anal cancer.

Results

A series of FFPE tissue samples of HIV+ men with anal cancer (n=26), AIN3 (n=24), AIN2 (n=42), AIN1 (n=22) and controls (n=34) were analyzed for DNA methylation of nine genes using quantitative methylation-specific-PCR. Univariable and LASSO logistic regression, followed by leave-one-out-cross-validation (LOOCV) were used to determine the performance for the detection of AIN3 and cancer.

Conclusion

Methylation of all genes increased significantly with increasing severity of disease ($p<2x10-6$). HGAIN revealed a heterogeneous methylation pattern, with a subset resembling cancer. Four genes (ASCL1, SST, ZIC1 and ZNF582) showed remarkable performance for AIN3 and anal cancer detection (AUC>0.85). The most potent marker, ZNF582 (AUC=0.89), detected all cancers and 54% of AIN3 at 93%

specificity. Slightly better performance (AUC=0.90) was obtained using a marker panel including five markers.

References

DNA methylation is significantly associated with anal carcinogenesis. A methylation marker panel, including ZNF582, can identify anal cancer and HGAIN with a cancer-like methylation pattern. Validation studies are warranted to verify their potential for the screening and management of HIV+ MSM at risk for anal cancer.

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00162

HPV Prevalence of Rectal and Scrotal Squamous Cell Cancers in the United States

25. Anal neoplasia

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Background / Objectives

Rectal squamous cell cancers (SCC) are morphologically similar to anal cancers and are thought to be caused by HPV. HPV was recently identified to cause some scrotal cancers. We determined the prevalence of HPV types in rectal and scrotal cancers in comparison with anal and penile cancers in the United States.

Results

The staff in three population-based cancer registries identified all or a sample of cases of invasive scrotal carcinomas, rectal SCC, and anal carcinomas newly diagnosed during 2014-15. One diagnostic tumor-containing block per case was serially sectioned for HPV detection and typing with confirmation of histology in sections preceding and following. L1 consensus PCR with type-specific hybridization was performed to identify 37 types. Overall and type-specific prevalence was determined. The preventable fractions of cancers were estimated based on the hierarchical proportion to HPV 16 and 18 oncogenic genotypes included in all vaccine formulations (HPV 16/18; 16/18) and the additional protection from the 5 new types in the 9-valent) vaccine (HPV 31/33/45/52/58: 5 types) Preliminary data were unweighted. We compared scrotal prevalence to penile prevalence from an earlier similar US study.

Conclusion

Samples from 72 anal, 41 rectal and 6 scrotal cancers were successfully genotyped. The prevalence of any HPV, HPV 16/18 and 5 additional types varied by anatomic site: Anal 96% [16/18:80.6%,5 additional: 8.3%]; Rectal 83% [16/18: 73.2%, 5 additional: 9.8%]; Scrotal 67% [16/18: 50%, 5 additional: 0%]. HPV prevalence of penile cancers (n=79) was 63% [16/18: 47.9%, 5 additional: 9.0%].

References

New estimates of HPV prevalence for rectal SCC are similar to anal carcinoma and that of scrotal carcinoma is similar to penile carcinomas. These estimates will be useful as a baseline measure to determine the future impact of vaccines on these two cancers.

00221

TOPICAL ABI-1968, AN ACYCLIC NUCLEOSIDE PHOSPHONATE PRODRUG FOR TREATMENT OF HPV-ASSOCIATED ANAL AND CERVICAL HSIL

25. Anal neoplasia

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Background / Objectives

ABI-1968 (Octadecycloxyethyl benzyl 9-[(2-phosphonomethoxy)ethyl]guanine) is an acyclic nucleoside phosphonate prodrug of PMEG-pp under development for topical treatment of anal and cervical high-grade squamous intraepithelial neoplasia (HSIL) caused by hr HPV infection. ABI-1968 has potent activity against diverse lr and hr HPV genotypes, inhibiting HPV DNA synthesis in a luciferase reporter gene assay (EC50 = 0.04 – 0.18 mM; CC50 >10mM). It has also been shown to be antiviral for productive HPV infection in 3D organotypic epithelial cultures causing DNA damage associated with induction of apoptosis in suprabasal strata (1, 2). ABI-1968 has been shown to induce DNA damage and arrest in S- and G2/M-phase and induction of apoptotic markers in HPV-transformed cells. The prodrug chemistry is designed to facilitate efficient transmembrane uptake into cells and controlled activation to PMEG-pp. We have used data from cellular uptake and metabolism studies of ABI-1968 and cidofovir (3) to model the integrated activation constants and intracellular elimination half-lives. The modeling reveals that ABI-1968 is activated 8-fold more slowly and has an extended elimination half-life of ABI-1968 relative to cidofovir. These properties should result in slower accumulation of the active drug species following topical treatment, potentially minimizing local toxicities and permitting less frequent yet effective dosing regimens.

Results

ABI-1968 topical cream has been studied in 40 healthy volunteers and more than 40 patients with either anal HSIL or cervical HSIL. In addition to tolerability of the cream, ABI-1968 activities are being demonstrated by histopathology and physician observations using colposcopy or high resolution anoscopy (HRA). Images from colposcopy or HRA have also been captured before and after treatment.

Conclusion

To date, weekly application of up to 5 doses is well tolerated at dosage strengths ranging from 0.01-1.0%. No dose limiting toxicities have been observed. Adverse events are generally mild and confined within the anogenital region. There have been no discontinuations due to adverse events. Preliminary changes in histopathology, lesion appearance and HPV status in these patients have been observed. No systemic exposure has been detected (assay LOQ = 0.2 ng/mL) and no systemic adverse events have been reported. Safety, PK and pharmacodynamic results will be further summarized.

References

Topical ABI-1968 is a potential topical treatment for HPV-associated HSIL. The preliminary pharmacodynamic observations and favorable clinical safety profile strongly support further development of ABI-1968 in both cHSIL and aHSIL.

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00248

PREVALENCE OF HPV AND ANOMALOUS ANAL CYTOLOGY IN HIGH-RISK WOMEN: A SINGLE-CENTRE STUDY

25. Anal neoplasia

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Background / Objectives

The appearance of anal intraepithelial neoplasia (AIN) and its progression to cancer is related to multiple factors. The identification of risk groups would allow an early diagnosis of the AIN, considering the inclusion of this location in the routine study (1,2).

The aim of this study is to compare the prevalence of Human Papillomavirus (HPV) and altered anal cytology in women with high-grade cervical dysplasia with respect to patients without injury or with low-grade injury. It has also been analyzed what other risk factors are significant.

Results

A prevalence study was conducted from April 2015 to March 2017. We recruited the new patients referred to the Pathology Unit of the Lower Genital Tract. Women diagnosed with CIN2+ were considered high risk; those without injury or CIN1 were considered low risk. Genotyping of HPV and anal cytology were performed. Those with abnormal anal cytology were referred to High Resolution Anoscopy. All included women completed a clinical questionnaire.

Conclusion

Of 171 patients recruited, 51 (29.8%) were diagnosed with CIN2+: there were no statistically significant differences in the prevalence of high-risk HPV (HR-HPV) (29% vs 30%, P = 0.9); nor in abnormal anal cytology (45% vs 27%, P = 0.1, OR 2.2, 95% CI 0.7-6.2) with respect to the low risk group.

The detection of cervical HR-HPV increases the risk of anal HR-HPV (OR 3.3, 95% CI 1.6-7.9, P < 0.05).

The prevalence of HR-HPV in immunocompromised patients, 14% of the population, is higher than in immunocompetent patients (20% vs 9%, OR 2.4, 95% CI 0.91-6.66, P < 0.05).

Predictive regression model that classifies 65.28% of the HR-HPV anal-positive population: immunosuppression (OR 4.9), cervical HR-HPV (OR 4.1), smoking (OR 0.2), P < 0.05; high grade dysplasia (OR 0.75); anal sex relations (OR 1.7), P > 0.05. S = 49%, E = 80%.

References

Other studies show the higher incidence of AIN and anal cancer in women with a history of invasive and in situ genital cancers (OR 1.82 to 16.4) (3,4,5). The appearance of high-grade AIN presents a latency of about 25 years in these patients (6). Based on our results, high-grade cervical dysplasia of recent diagnosis does not appear to be an independent risk factor for the detection of abnormal anal cytology and anal HR-HPV, but the state of immunosuppression is associated with anomalous results (7,8).

More evidence is needed to clarify the relationship between cervical and anal HPV infections; as well as the effect of the different shared risk factors.

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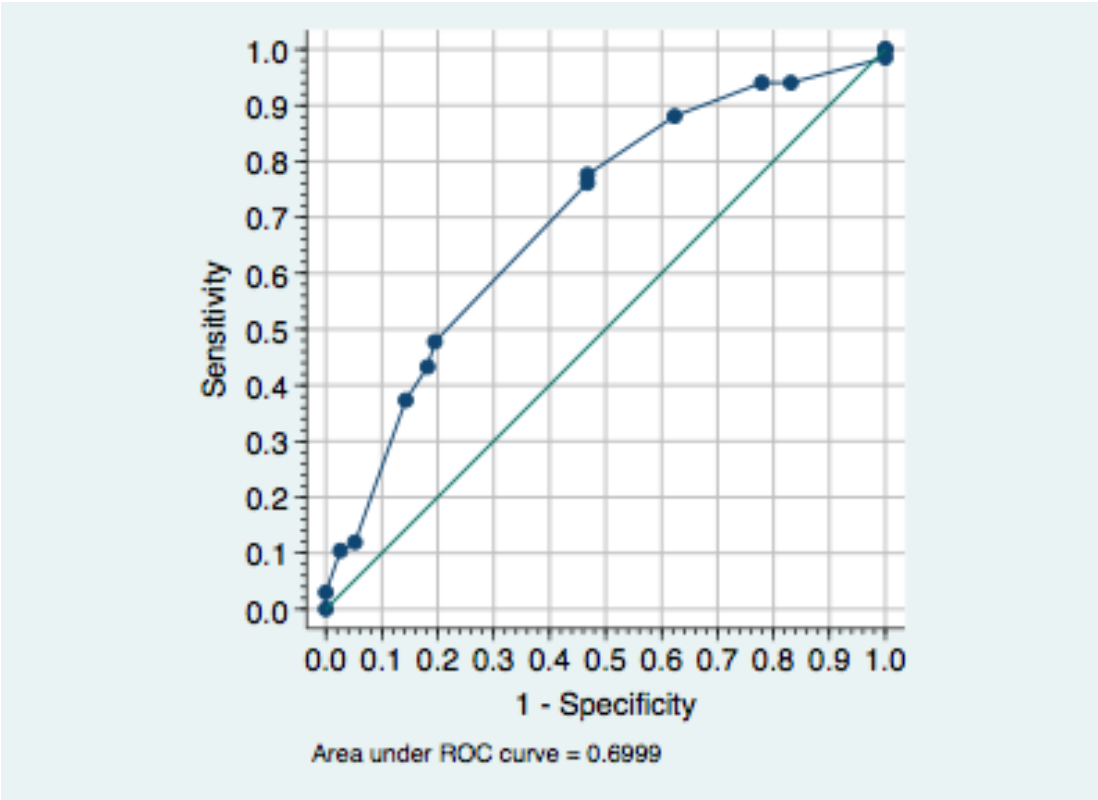

00499

SYSTEMATIC REVIEW AND META-ANALYSIS ON THE PROGNOSTIC SIGNIFICANCE OF p16INK4A AND HIGH-RISK-HPV DNA IN ANAL SQUAMOUS CELL CARCINOMA

25. Anal neoplasia

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Background / Objectives

Oncogenic human papillomavirus (HPV) types are assumed to play an etiological role in a major proportion of anal squamous cell carcinomas (ASCC). The etiological association is indicated by the detection of high-risk HPV (HR-HPV) DNA, which has been detected in up to 90% of ASCC in previous studies, and the cell cycle regulator protein $p16^{INK4A}$. By analogy to other HPV-driven tumor entities, it has been suggested that these two markers are of prognostic significance in ASCC. However, the published studies have reported heterogenous survival data stratified by these two markers and clinical variables.

Our systematic review and meta-analysis aims to determine the prognostic relevance of oncogenic HPV DNA, $p16^{INK4A}$, and clinical characteristics in ASCC.

Results

Published studies analyzing $p16^{INK4A}$ and survival in ASCC were identified by a broad search string. Authors of included studies were contacted to obtain individual patients' data (IPD). Overall survival (OS) was analyzed by Cox-Regression analyses using $p16^{INK4A}$ and HR-HPV DNA status with adjustment for relevant covariates.

Conclusion

Sixteen studies were initially identified. We received IPD from eight studies with a total of 666 patients diagnosed with an ASCC. 544 patients could be included in further analyses. 451 of a total of 538 ASCC (83.8%) overexpressed $p16^{INK4A}$ on immunohistochemistry. In 82.0% of 460 ASCC HR-HPV DNA was detected. Compared to patients with both $p16^{INK4A}$- and HR-HPV DNA-positive ASCC patients with an ASCC negative for $p16^{INK4A}$ and HR-HPV DNA had the worst OS (HR=3.3 (95% Confidence Interval (CI), 2.0-5.4), $p<0.001$) in a multi-variable analysis. Patients with discordant $p16^{INK4A}$ and HR-HPV DNA status differed regarding survival. Patients with $p16^{INK4A}$-positive, but HR-HPV DNA-negative ASCC had a worse OS than patients with a $p16^{INK4A}$-negative, but HR-HPV DNA-positive ASCC (HR=2.9 (95% CI, 1.6-5.3), $p<0.001$ and HR=2.6 (95% CI, 1.3-5.1), $p=0.005$, respectively) compared to patients with HR-HPV DNA- and $p16^{INK4A}$-positive ASCC.

References

Our systematic review and meta-analysis demonstrates that simultaneous HR-HPV DNA detection and $p16^{INK4A}$ overexpression are found in the majority of ASCC and predict a better OS. However, a combination of markers is necessary to reliably assess the prognosis of affected patients.

00307

ANAL AND ORAL HUMAN PAPILLOMAVIRUS INFECTIONS IN THE NEW ERA OF HIV-PrEP'S USERS

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

Human Papillomavirus (HPV) infection is the first sexual transmitted infection (STI) worldwide and plays a major role in the development of cervical, anal and oropharyngeal cancers. One of the main risk factors described for pathogenicity is the local persistence of high-risk HPV types (hrHPVs).

Results

We conducted a prospective study single-center between May 2017 and August 2018 to assess prevalence, persistence and type of anal and oral HPV infections in a cohort of men who have sex with men (MSM) on HIV pre-exposure prophylaxis (PrEP).

Patients characteristics, anal and oral swabs (UTMTM Copan) were collected at first medical consultation (D0) and six months later (M6). Extracted DNA was amplified with AnyplexII HPV28 kit (Seegene®) allowing the detection of 19 hrHPVs and 9 low-risk HPV types (lrHPVs). GraphPad software was used to perform Spearman rank and Fisher test.

Conclusion

Fifty-eight participants were enrolled and median [IQR] age was 36 [18-74] years. Median number of different partners was 5 [1-35] per month with around 40% of anal intercourse condom-free and 18 (31%) participants used oral drugs during sex. None had been HPV vaccinated before starting PrEP. Thirty (52%) participants had previous STIs, 12 (21%) a history of condyloma and 12 (21%) at least one STI the day of HPV sampling. At D0, at least one HPV type was detected in 53 (91%) anal samples but only in 2 (3.4%) oral samples. A median of 3 [0-8] different HPV per sample was detected from anal swabs; the most prevalent hrHPVs were HPV59 (26%), HPV51 (17%) and HPV16-68-73 (each of them at 16%) and the most prevalent lrHPVs were HPV6 (26%) and HPV42 (26%). Overall, hrHPVs were found in 48 (83%) participants with a median of 2 [0-6] different hrHPVs per sample. Among them, 27 (56%) participants had at least one hrHPV covered by the 9-valent HPV vaccine. The number of hrHPVs was weakly correlated with the PrEP use duration (r_s=0.32 p=0.013) and history of STIs was a risk factor for hrHPV infection (Odd ratio=6.44, 95% CI 1.23-31.79, p=0.032). Among the 12 participants tested at M6, persistence of at least one hrHPV occurred in 9 (75%) cases. The number of different partners and hrHPV persistence were positively correlated (r_s=0.604 p=0.037).

References

This study shows a high prevalence of hrHPVs in anal samples from PrEP users, associated with the duration of PrEP and previous STIs. Although HPV infection persistence has been assessed on few patients, regular proctologic examination should be offered in order to detect associated lesions. The benefit of HPV vaccination before starting PrEP might be discussed.

FC 10. Diagnostics & management 1

00184

High correlation between clearance of High-Risk HPV strains after LLETZ and absence of residual disease in patients with early stage cervical cance

08. HPV testing

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Background / Objectives

: The standard treatment for early-stage cervical cancer is radical hysterectomy and pelvic or para-aortic lymphadenectomy. We examined whether, in patients with cervical cancer stage I A 1-I B 1, positive for High-Risk HPV (HR-HPV), clearance of the viral DNA after large loop excision of the transformation zone (LLETZ) has a high correlation with absence of cervical cancer at the final pathological specimen.

Results

Data was collected about 54 patients diagnosed with invasive cervical cancer (stage IA1- IB 1) and positive HR-HPV DNA. Shortly after the LLETZ a repeat HPV-HR test was done, before the final surgical treatment. We compared characteristics of patients with negative or positive HR-HPV from the cervix, and investigated the association of post-LLETZ HR-HPV status with residual cancer on final pathology.

Conclusion

Of 54 patients, 20 were HR-HPV negative post-LLETZ; 16(80%) had normal histology on the final pathological sample, 2 (10%) had CIN 3, and only 2(10%) had residual cancer in the final pathological specimen

Of the 34 women who were positive to HR-HPV, 8 (23.5%) were sent to chemo-radiation .The other were operated and final histological result was invasive cancer in 14 (41.2%), CIN 3 or AIS in 8(23.5%) and normal histology in 4(11.8%) women.

References

: Clearance from the cervix of HR-HPV post-LLETZ has a high correlation with the absence of residual cancer in the final surgical specimen. More studies are needed to prove if negative HR-HPV after LLETZ might serve as a new parameter for risk assessment and for less aggressive surgery in women with early stage cervical cancer.

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00532

ROLE OF DNA HPV TEST IN THE FOLLOW-UP OF WOMEN UNDERGOING EXCISIONAL SURGICAL PROCEDURES OF CERVICAL CANCER PRECURSOR LESIONS

08. HPV testing

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Background / Objectives

The evaluation of the best methods for follow treatment and a broad knowledge of the risk factors associated with greater chance of relapse are critical to achieving the best rates of successful treatment of cervical cancer precursor lesions and avoid more invasive procedures. OBJECTIVE:Evaluate the role of HPV DNA screening in the follow-up of patients submitted to excisional surgical procedures for the treatment of cervical cancer precursor lesions in the Lower Genital Tract Pathology Service of the Gynecological Clinic Division of the Hospital das Clínicas, Faculdade de Medicina da University of Sao Paulo

Results

Retrospective Cohort

Conclusion

About 85% of the patients who do this control have negative results. Other data are analyzed.

References

The possibility of post-treatment control of precursor lesions of cervical cancer with fewer and shorter exams is proving to be an excellent method for life control and the motility of this alteration. Several countries have already instituted this monitoring method with proven good results.Here we present the experience of a public hospital with limited resources in a population with low socioeconomic status

00040

JUSTIFYING CONSERVATIVE MANAGEMENT OF CIN2 IN WOMEN

20. Diagnostic procedures / management

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Background / Objectives

In 2012 the guideline from the Society of Obstetricians and Gynaecologists of Canada and the Society of Canadian Colposcopists (SOGC/SCC) changed from immediate treatment to a conservative management of CIN2 in young women [1,2]. In this study, the outcomes before and after this guideline change were reviewed in Nova Scotia, Canada.

Results

A retrospective population-based cohort study was performed among women younger than 25 years with Cervical Intraepithelial Neoplasia (CIN) grade 2, who were referred to colposcopy clinics in Nova Scotia between 2010-2014. Regression, persistence and progression rates were compared pre- and post-guideline changes.

Conclusion

Of the 636 women included in the study, 286 women were diagnosed with CIN2 before and 350 women after the guideline was changed. Women in the post-guideline period had significant more chance of a conservative approach (78.6% versus 44.1%; $p<0.001$), whereas 73.4% of the women in the pre-guideline period underwent treatment during follow-up compared to 38.9% in the post-guideline group ($p<0.001$). Regression occurred in 73.1% of all women, but women seen in the post-guideline period had a higher regression rate and lower progression rate ($p<0.05$). Histologic results from treatment specimen did not show a significant difference in

low-grade or high-grade lesions before or after the guideline has been changed (p0.59).

References

Conservative management seems safe and thus a justified approach for women younger than 25 years with CIN2.

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00133

OUTCOMES OF CONSERVATIVE MANAGEMENT IN WOMEN WITH TRANSFORMATION ZONE EXCISION (TZE) SPECIMENS WITH POSITIVE MARGINS

20. Diagnostic procedures / management

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Background / Objectives

In the past, appropriate management of positive margins after TZE was considered to be re-excision or even hysterectomy. Most recent recommendations advocate close surveillance in selected cases.

Our objective was to evaluate the outcomes of a case series of women with positive margins after TZE, managed conservatively, 24 months after the treatment.

Results

We performed a retrospective cohort analysis of all the cases of TZE with positive margins (CIN2+), between 2011 and 2018. We analysed the results of Pap tests, HPV tests (cobas®), colposcopies and biopsies, when performed. We considered “cured” the women with a Pap test ≤ASC-US, negative HPV test, normal colposcopy or biopsies ≤LSIL at 24 months. Evaluation at 6, 12 and 18 months was also performed.

Conclusion

Out of 201 cases of HSIL in the TZE specimen, 28 had positive margins (13.9%). We excluded 12 cases: 7 for invasive cancer, 1 had a total hysterectomy due to genital prolapse, 2 were lost to follow-up and 3 that have less than 24 months of follow-up. A total of 6 cases (60%) were considered cured, re-excision of transformation zone was performed in 5 (33%), and one (7%) is still under surveillance (positive HPV test).

The women considered cured at 24 months of follow-up were younger (35,7±5.77 vs. 41.6±11.57 years, p=0.22). On the other hand, 20% of the cases that required re-excision were post menopausal (p=0.16).

There were no differences according to the technique used (electrosurgical loop or needle excision). All cases submitted to re-excision of the transformation zone (TZ) had endocervical involvement(100% vs.66,7%, p=0.19).

A positive HPV test at 6 or 12 months was associated with the need of performing a re-excision of the TZ (33% vs. 100%, p=0.035 and 50% vs. 100%, p=0.035, respectively).

Moreover, a Pap test worse than ASC-US at 6 or 12 months was also associated with re-excision of the transformation zone (75.0% vs. 16.7%, p=0.07 and 80%vs. 11.1% of the cured, p=0.01, respectively).

References

In our series, we observed that 60% of the cases of TZE specimens with positive margins were disease free at 24 months. The need for further treatment was higher in older women, and in those with a positive HPV test and/or a Pap test > ASC-US at 6 and 12 months.

00267

IS HIGH RISK HUMAN PAPILLOMAVIRUS (HR-HPV) TESTING RELIABLE FOR THE FOLLOW UP OF WOMEN TREATED FOR GLANDULAR NEOPLASIA AND MICRO-INVASIVE CANCER

20. Diagnostic procedures / management

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Background / Objectives

The high sensitivity of Hr-HPV testing has led to its use in post-treatment follow up protocols as a “Test of Cure” (ToC) following treatment of CIN. This practice has reduced the intensity and extent of follow up, permitting a more rapid return to routine recall for the majority of women. Women treated for micro-invasive cancer (MIV) and glandular lesions generally have intense follow up and in the latter group, a greater potential of an inadequate smear due to absent endocervical material. There are little data on whether Hr-HPV testing as a ToC would be of value in these groups.

The objective was to determine utility of HPV testing as a ToC following treatment for cervical glandular lesions and MIV

Results

In Scotland, standard care for women treated for glandular neoplasia and MIV is to return to colposcopy at 6 and 12 m with smears, followed by 4 annual community smears. For this project, eligible women were those who had been treated for microinvasive squamous or adenocarcinoma, glandular abnormality (CGIN) or stratified mucinous intraepithelial lesion (SMILe). Hr-HPV testing was performed on the smears taken at 6 and 12 m post-treatment although standard care was not influenced in this observational project. Recruitment was from 2014-2016. As the main outcome was presence/absence of disease within 3 years, we present an interim analysis on those women for whom we have follow up for at least 2.5 years.

Conclusion

A total of 667 individuals were included in the cohort; 175 had at least 2.5 years follow-up from the 6 month post treatment Hr-HPV test. A total of 38/175 were treated for MIV (5 adeno; 33 squamous) and the remainder for pre-invasive glandular

lesions. Hr-HPV positivity at 6 m post-treatment was 23.6% and 14.6% in women treated for MIV and glandular lesions respectively. During follow up 7 high grade lesions were confirmed, 6 following treatment for pre-invasive glandular lesions and for 1 for MIV. Overall, specificity and PPV of a Hr-HPV test at 6 m post treatment for MIV were 78.3% (61.3%-89.6%) and 11.1% (5.8-49.3%). For preinvasive glandular lesions these values were 87.8% (80.1%-92.6%) and 20.0 (6.6%-44.2%). Sensitivity and NPV of Hr-HPV testing for MIV were 100% (5-100%) and 100% (85.4-100%) while for glandular lesions were 66.6% (24.1%-94.0%), and 98.3 (93.3%-99.7%).

References

This is an interim analysis and we await 3 year outcomes on the complete cohort. However, initial results suggest that the performance of HPV testing as a ToC after treatment for glandular abnormalities might lack the level of clinical sensitivity observed during the follow up of squamous lesions.

00147

Colposcopy Evaluation at the Time of LEEP May Avoid Unnecessary Treatment

21. Colposcopy

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Background / Objectives

The aim of the study was to assess the accuracy of colposcopy evaluation at the time of the loop electrosurgical excision procedure (LEEP) to identify women with a previous confirmatory diagnosis of squamous intraepithelial lesion/cervical intraepithelial neoplasia (SIL/CIN) with low probability of dysplasia in the LEEP specimen.

Results

We prospectively recruited a cohort of 162 women undergoing LEEP for histological high-grade SIL/CIN 2–3 or lowgrade SIL/CIN 1 with high-grade SIL cytology showing a fully visible squamocolumnar junction in the colposcopy evaluation at the time of LEEP. At the referral visit cervical cytology, human papillomavirus and genotype detection, digital colposcopy, colposcopical lesion measurement, and 1 or more biopsies of the transformation zonewere obtained. The uterine cervix was colposcopically evaluated intraoperatively.

Conclusion

Thirty-four women (21.0%) had a normal colposcopy evaluation at the time of the LEEP,whereas the remaining 128women showed abnormal findings. Absence of SIL/CIN in the LEEP specimen was confirmed in 28 (82.3%) of the 34 women with a normal colposcopy at the time of LEEP group and 8 (3.1%) of the 128 women showing abnormal colposcopy at the time of LEEP group ($p < .001$). A normal colposcopic evaluation at the time of LEEPwas associatedwith an increase in the risk of absence of lesion in the cone specimen compared with cases presenting an abnormal colposcopy (95% CI = 33.8–1,555.1, $p < .001$). The colposcopy evaluation at the time of LEEP had a positive predictive value of 82.3% (95% CI = 66.5–91.5)

and a negative predictive value of 96.9% (95% CI = 92.2–98.8) to predict low probability of SIL/CIN in the specimen.

References

Colposcopic evaluation at the time of LEEP seems to be accurate to identify SIL/CIN postbiopsy regression; thus, its performance would be considered at the time of the treatment

References

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00200

COLPOSCOPIC AND HISTOPATHOLOGIC EVALUATION OF WOMEN AGED 56-64 WITH HPV-PERSISTENCE 1 AND 3 YEARS, RESPECTIVELY, FROM THE ORGANIZED PRIMARY HPV SCREENING IN SWEDEN.

21. Colposcopy

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Background / Objectives

The aim of this study was to evaluate the colposcopic and histopathologic findings in HPV++ women age 56-64 years in an organized primary HPV screening program.

Results

Starting in 2012, the organized screening program in Stockholm randomised all resident women 56-64 years to either primary HPV screening with cytology triage or to primary cytology and HPV triage. In the HPV arm, HPV positive/cytology negative (HPV+/Cyt-) women had a repeat HPV test 1 or 3 years later. All women with HPV persistence were referred to colposcopy performed by the same expert colposcopist.

Conclusion

Among 82 women who underwent colposcopy after 1 year, 66% (54/82) had a type-specific HPV persistence and 20% were persistent for HPV 16. 42% (34/82) had a transformation zone (TZ) type 3, 51% (42/82) had atrophy, 12/82 (15%) had an abnormal cytology from the endocervix and 22% (18/82) had a HSIL in histopathology. Among 45 women who underwent colposcopy after 3 years, 58% (8/45) had a type-specific HPV persistence and 18% were persistent for HPV 16. 58% (26/45) had a TZ type 3, 64% (29/45) had atrophy, 19/45 had an abnormal cytology from the endocervix, and 7/45 had a HSIL in histopathology.

References

Colposcopic and histopathologic findings were similar for women after 1 year and 3 years of HPV persistence. TZ type 3 and atrophy is a challenge and blind as well as diagnostic cone biopsies, HPV genotyping and cytology triage are options for follow up of this group.

00402

COLPOCONNECT: USER-CENTERED DEVELOPMENT FOR A HEALTHCARE APP TO DECREASE BARRIERS TO COLPOSCOPY ATTENDANCE IN A RURAL CANADIAN SETTING

21. Colposcopy

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Background / Objectives

Numerous healthcare applications are developed each year with only a small proportion found useful to the intended users. The ColpoConnect App prototype was developed to address barriers in accessing colposcopy in northern Canada after referral for abnormal cervical cytology, and to provide a direct link for women to healthcare providers (HCP). Significant human resource and geographical challenges contribute to increased morbidity from cervical dysplasia in this underserviced population. The study objective was to collect insight from intended users to support app design incorporating known barriers to care in our rural population.

Results

A survey of women attending colposcopy (n=44) and a retrospective chart review (n=309) were done, reviewing access to colposcopy, access to technology, and barriers to attendance. The app prototype was developed using this data and employing user-centered principles through a “Hacking Health” tech start-up/population health collaboration. Low health literacy and low bandwidth functionality were optimized based on user needs. To advance app development, women were then recruited for semi-structured interviews at the time of colposcopy (n=7). Interview questions examined: hypothetical scenario with abnormal pap result,

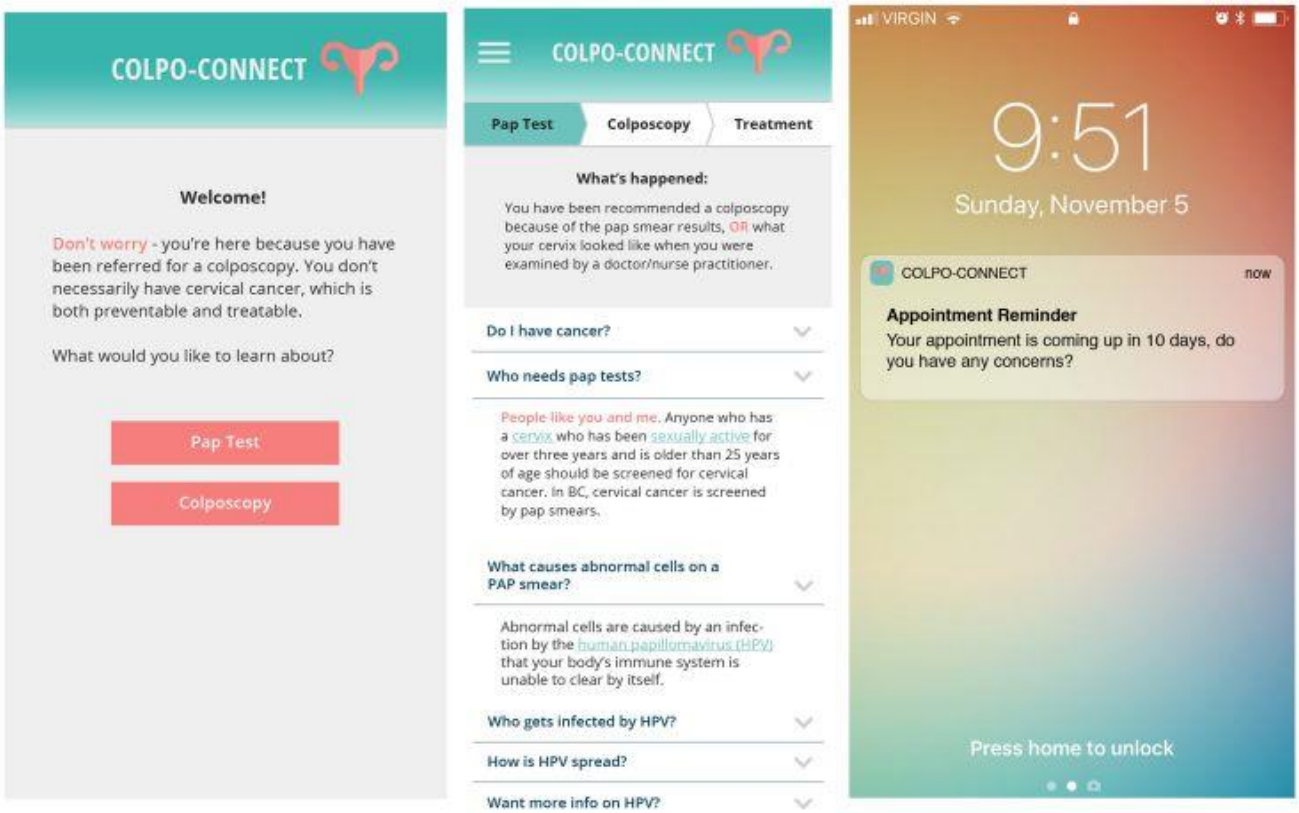
health communication, internet usage, health literacy, and initial impressions of the app prototype. Themes and sub-themes were identified from interview transcripts using Nvivo software.

Conclusion

The chart review found 25% of women referred for colposcopy did not attend their first appointment, while the patient survey showed over 77% indicating significant anxiety about their appointment, and 23% reporting no or very little knowledge of colposcopy. Further, 61% wanted to access more information and to directly connect with HCPs through text messages and phone calls. User impressions of the app were positive regarding ease of use and the inclusion of appointment reminders and themes around addressing lack of knowledge and anxiety were addressed.

References

Patient anxiety and limited knowledge are major barriers to colposcopy attendance. The ColpoConnect App aims to address anxiety by providing health information and individualized support. Providing an interface between HCPs and women referred for colposcopy is critically important in underserviced rural areas; and is crucial to improving colposcopy attendance in rural Canada with potential applications across diverse urban jurisdictions that may also be underserviced.


COLPO-CONNECT
Welcome!
Don't worry - you're here because you have been referred for a colposcopy. You don't necessarily have cervical cancer, which is both preventable and treatable.
What would you like to learn about?
Pap Test
Colposcopy
COLPO-CONNECT
Pap Test
Colposcopy
Treatment
What's happened:
You have been recommended a colposcopy because of the pap smear results, OR what your cervix looked like when you were examined by a doctor/nurse practitioner.
Do I have cancer?
Who needs pap tests?
People like you and me. Anyone who has a cervix who has been sexually active for over three years and is older than 25 years of age should be screened for cervical cancer. In BC, cervical cancer is screened by pap smears.
What causes abnormal cells on a PAP smear?
Abnormal cells are caused by an infection by the human papillomavirus (HPV) that your body's immune system is unable to clear by itself.
Who gets infected by HPV?
How is HPV spread?
Want more info on HPV?
VIRGIN
9:51
Sunday, November 5
COLPO-CONNECT
now
Appointment Reminder
Your appointment is coming up in 10 days, do you have any concerns?
Press home to unlock

00406

TEST OF CURE AFTER LEEP FOR CERVICAL INTRAEPITHELIAL NEOPLASIA

21. Colposcopy

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Background / Objectives

The most common treatment modality nowadays for cervical intraepithelial neoplasia (CIN) is loop electrosurgical excision procedure (LEEP). The test of cure after LEEP in Finland has the last decades been a follow-up colposcopy with a Pap-smear and the last years also a hrHPV-test 6 months after the procedure. The aim of our study was to compare colposcopy, cytology and highrisk-HPV (hrHPV) as a test of cure after LEEP.

Results

The study was conducted as a part of a large prospective cohort study. Patients were recruited at the Helsinki university hospital colposcopy unit during 2014-2016. All patients who had a LEEP procedure (n=462) were included. Patients were followed-up at six months by colposcopy, hrHPV-test, pap-smear and biopsies when needed.

Conclusion

Preliminary results

16.5% of the patients (n=76) were hrHPV positive at six months follow-up. Of these HPV positive patients 15.8 % (n=12) had CIN1+ and 3,9 % (n=3) had HSIL (CIN2+) in colposcopy guided biopsies. Majority of the patients (83.5 %, n=386) were hrHPV negative at six months. Of these (96.1 %, n=371) had also a negative histology. Of the hrHPV negative patients only 3,9 % had a mild histological finding of (CIN1, VIN1 or VAIN1) negative predictive value (NPV) 0.96 (95% CI 0.94-0.98) but none had HSIL histology at colposcopy NPV 1 (95% CI.0.99-1).

References

Colposcopy as a test of cure is time and resource consuming. Our findings suggest that performing colposcopy for only hrHPV positive patients could be an alternative approach and using hrHPV testing together with papsmear at 6 months provides a reliable test of cure. A longer follow-up period is needed to evaluate the natural history of hrHPV infection after LEEP.

00498

THE ROLE OF SWEDE SCORE AND MODIFIED REID COLPOSCOPIC INDEX IN THE PREDICTION OF CIN3+ LESIONS

21. Colposcopy

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Background / Objectives

Colposcopic scoring indices provide an objective tool in the diagnosis of cervical pathologies. The basic systems include Reid's colposcopic index with its variants and the Swede score and the latest modality. The aim of our study was to evaluate the significance of these indices in the prediction of CIN3+ lesions.

Results

Between years 2015-2017 we evaluated 386 patients, who underwent the colposcopic examination due to the suspicious cytological finding (ASCUS – 77 (19.9 %), LSIL – 182 (47.1 %), ASC-H - 39 (10.1 %), HSIL - 71 (18.4 %) a AGC – 17 (4.4 %)). HPV status was verified by the HC2 (Hybrid Capture® 2 test) and the colposcopic finding was scored by colposcopic indices for every patient included in our study. Subsequently we analysed the sensitivity, specificity and positive and negative predictive value of the indices for the detection of CIN3+ lesions compared to HPV assay. We excluded the patients after the surgical procedure on the uterine cervix in the past and also pregnant women from the statistical analysis.

Conclusion

Modified Reid colposcopic index with the cut-off value ≥4 showed the sensitivity 86.67 % (95% CI: 77.9 – 92.9) and specificity 81.08 % (95% CI: 76.1-85.4) for the detection of CIN3+ lesions. Swede score at the cut off value ≥ 6 achieved comparable parameters for CIN3+ lesions: sensitivity 88.65% (95% CI: 82.2 - 93.4), specificity 89.39% (95% CI: 84.8 - 92.9). Although the sensitivity of HPV DNA test showed better results compared to colposcopic diagnostics in CIN3+ lesions : 96.1%

(95% CI 89.0-99.2), the specificity was very low: 30.0% (95% CI: 23.6 - 37.1). There were no statistically significant differences between Swede score and Reid index in CIN3+ detection.

References

Swede score as a relatively new colposcopic scoring system showed in our study the best combined sensitivity and specificity in the detection of CIN3+ lesions. Both scoring systems, however, confirmed the high efficiency in the differential diagnosis of cervical pathologies. Combination of colposcopy and molecular biology methods together with the HPV DNA testing could further increase the accuracy of non-invasive screening of cervical dysplasia.

00524

The role of colposcopy at twelve months after excision of the transformation zone

21. Colposcopy

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Background / Objectives

International and national guidelines regarding the follow-up of women after LLETZ (large loop excision of the transformation zone), recommends colposcopy and cytology at 6 months. At 12 months, cytology and HPV testing are recommended and then yearly, until two consecutive negative results. However, colposcopy at 12 months remains common practice. The aim of this study is to: i) analyze outcomes from LLETZ procedures carried out for higher-grade cytology (atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion [ASC-H] or high-grade squamous intraepithelial lesion [HSIL]) associated with high-grade intraepithelial neoplasia (CIN2+) or with abnormal colposcopy findings; and ii) to assess the role of colposcopy in the management of women at 12 months.

Results

A retrospective analysis was performed of 110 women who had undergone a LLETZ procedure between January 2015 and December 2016. Demographic variables; pre-LLETZ citology and cervical biopsy results; histological results of LLETZ, maximum depth of tissue obtained and margins status; citology, cervical histology, colposcopy findings and HR-HPV test result, taken in the 2 years after LLETZ; were collected.

Conclusion

One hundred and ten LLETZ procedures were carried out. Exclusions included LLETZ for reasons other than higher-grade cytology ± CIN2+ and women diagnosed with cancer. The median age was 37,8 years with 8,8% aged over 50 years. 16,1% were nulliparous and 8,9% postmenopausal. 22,5% of women were current smokers and 60,8% were using hormonal contraception (42,2% oral pill). HPV vaccination pre-LLETZ was positive for 5,9%. Prior to LLETZ 77,4% of women had higher-grade cytology and 85,3% had CIN2+ on targeted cervical biopsy. LLETZ confirmed 80,4%

high-grade dysplasia detected on citology. Complete excision was documented for 73,7% of cases with a mean depth of 9,1mm. Regarding incomplete excision, 81,5% had an endocervical margin with dysplasia. 96,1% of patients attended their first follow-up (6 months): 12,2% had a aceto-white epithelium (AWE) and in 18,4% of colposcopies squamocolumnar junction (SCJ) was not visualized (TZ3). 20,4% of women had an abnormal cytology (≥ASC-US) at 6months and 11,3% at 12 months. 95,1% attended the 12 month visit: 21,6% of colposcopies classified SCJ as TZ3 and AWE in 14,4%. Most women had a HR-HPV test done with a positive rate of 16,5% (HPV 31 – 37,5%; HPV 16 – 31,2%). The sensitivity of colposcopy at 12 months was 0,5 and the specificity was 0,95.

References

Colposcopy after LLETZ is an examination with low sensitivity. It increases false-positive rates for high-grade lesions, potentially exposing women to anxiety and futher procedures. The high rate of SCJ not visualized after LLETZ, reduces even more the role of colposcopy at twelve months after LLETZ.

00123

HSIL in pregnancy –Observation or LLETZ in the first 15 weeks The safety of LLETZ in the first 15 weeks of pregnancy

22. Cervical neoplasia

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Background / Objectives

Large Loop Excision of The Transformation Zone (LLETZ) is the recommended treatment in women diagnosed with CIN 2 or CIN 2-3 lesions. During pregnancy observation is recommended because of the belief that during pregnancy there is no progression to malignancy and the treatment is associated with severe complications. Summarizing data from literature pregnant women over the age of 25 years with CIN 2-3 lesions has a risk of 7.4% to be diagnosed with invasive cervical cancer after delivery.

We aimed to describe the Israeli experience in pregnant women diagnosed with CIN 2 or CIN 2-3.

Results

This was a multi-center trial in which we collected data of 140 pregnant women who were diagnosed with CIN 2 or CIN 2-3 between January 2006 and May 2018.

Conclusion

Of the 27 women with CIN 2 who were observed, CIN 2-3 was diagnosed in 25%. Of the 113 women with CIN 2-3 , 63 women were followed and 50 underwent LLETZ during pregnancy. In 63 women who were evaluated after delivery the final pathological results was as follow: 4 (6.4%) were diagnosed with cervical cancer, 43 (68.2%) had CIN 2-3, 16 (25.4%) had CIN 1 or normal histology.

Of the 50 women who underwent LLETZ during the 15 weeks of pregnancy invasive cancer was diagnosed in 3(6%), CIN 2-3 or AIS in 44 women (89%) and 3 patients (6%) had CIN 1 or normal histology.

Forty three women continued their pregnancy, 39 (90.7%) of them had term deliveries, two (4.6%) had late premature deliveries (34, 36 weeks) and two women (4.6%) had missed abortion after the LLETZ.

References

The risk of cervical cancer is 6.2 % in pregnant women with CIN 2-3 diagnosed during pregnancy.

The LLETZ procedure during the first 15 weeks of pregnancy is safe. Complications included: severe bleeding, abortion, and late premature delivery in low rates , similar to the general population.

We suggest reconsidering the indications regarding CIN2-3 treatment during pregnancy in patients older than 25 years old, and consider performing LLETZ more liberally during the first trimester as it has been shown to carry minimal risks and significant benefits.

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00288

INCIDENCE OF CERVICAL CANCER AND OTHER CANCERS AFTER TREATMENT OF CIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

22. Cervical neoplasia

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Background / Objectives

An increasing body of retrospective observational studies and meta-analyses suggests that CIN treatment, particularly excision, adversely affects future reproduction and the risk of prematurity(1-6). The frequency and severity of the observed adverse events is higher for the more radical techniques and with increasing cone length(1,5,7-12). This knowledge together with the ease of execution in more recent techniques like LLETZ have led to a progressive reduction in the radicality and depth of treatment.

Although all treatment techniques are highly effective in preventing recurrent pre-cancerous disease(13), several studies have documented an increase in the

incidence of cervical cancer after CIN treatment for up to 20 years post treatment. Some authors raise concerns that the progressive reduction in the radicality of treatment has led to this increased risk of future of invasion(14,15), while others advocate the move to less radical techniques for the prevention of treatment-associated perinatal morbidity and mortality(5).

Results

Design:Systematic review and meta-analysis.

Data Sources:MEDLINE, EMBASE and CENTRAL.

Eligibility Criteria:Studies with centralised follow-up assessing invasive cervical or other cancer incidence or mortality after treatment of CIN.

Data Extraction and synthesis:Pooled effect estimates for relative and absolute incidence rates were estimated using the inverse variance random-effects model with the Paule-Mandel method and between-study heterogeneity was measured using the Cochran's Q and I^2 statistics. The raw absolute incidence estimates were calculated using the variance-stabilising Freeman-Tukey double arcsine transformation. Risk of bias assessment was performed using the Quality in Prognosis Studies (QUIPS)-tool.

Main outcomes:Relative and absolute invasive cervical cancer incidence; relative incidence of other HPV-related genital tract cancer (vagina, vulva and anus), total cancer and mortality.

References

Women treated for CIN have increased incidence of not only cervical, but also of other HPV-related female genital tract cancers compared to the general population, for over 20 years after treatment. The risk is highest amongst women over the age of 50. Mortality from cervical and vaginal cancer combined is also elevated. A prolonged follow-up after the end of organised screening may be warranted for these women.

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FC 11. Vaccines 3

00046

HPV vaccine for women undergoing excisional treatment for HSIL/CIN2-3: role in the reduction of the risk of persistent/recurrent intraepitelial lesions

05. HPV prophylactic vaccines

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Background / Objectives

Up to 25% of the women treated for high-grade cervical intraepithelial lesion (HSIL/CIN2-3) present persistent/recurrent disease. Recent studies have shown preliminary evidence that a high title of antibodies against HPV could decrease the risk of recurrence in patients treated for HPV-related lesions. We aimed to provide insight into the role of HPV vaccination of women undergoing treatment for HSIL/CIN 2-3 to decrease the risk of persistence/recurrence

Results

Ninety-three women treated for HSIL/CIN2-3 from July 2016 to July 2017 were included. Vaccination was recommended to all women at the moment of HSIL/CIN2+ diagnosis. All patients were treated using Loop Electro-Excision Procedure (LEEP). First visit after LEEP was performed at three months. From then, patients were followed-up every 6 months up to 24 months with cytology (Thinprep), HPV testing (Cobas), colposcopy and biopsy of necessary. The main outcome was histological SIL diagnosis confirmed during the follow-up visits (persistent/recurrent disease)

Conclusion

Forty-one of the women included (41/93; 44.1%) underwent HPV vaccination. First dose of the vaccine was provided between HSIL/CIN2+ diagnosis and four months after treatment either with 2-valent or 4-valent HPV vaccine. Margins were positive in 26.8% (11/51) of the cone specimens from the vaccinated women and 21.2% (11/52) of the cone specimens from the not-vaccinated women (p=0.346). No persistent/recurrent disease was diagnosed within the vaccinated women. Within the women who had not received the HPV vaccine, persistent/recurrent disease was diagnosed in 1.9% (1/52) of them (p=0.559). Mean time to persistent/recurrent disease diagnosis was 24 month

References

First generation HPV vaccines might reduce the risk of recurrent/persistent disease in women treated for HSIL/CIN2+ lesions. Larger well-designed studies to answer the question
as to the value of HPV-profilactic vaccine in the reduction of the risk of persistent/recurrent are warranted

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00056

IMPACT OF HPV VACCINATION WITH GARDASIL® IN SWITZERLAND

05. HPV prophylactic vaccines

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Background / Objectives

Gardasil®, a quadrivalent vaccine targeting low-risk (6, 11) and high-risk (16, 18) human papillomaviruses (HPV), has been offered to 11-14 year-old schoolgirls in Switzerland since 2008. The aim of our study was to evaluate its success and potential impact on cervical cancer screening, examining HPV genotypes in 18-year-old girls five years later (sub-study 1) and in outpatients participating to cervical cancer screening before and after vaccine implementation (sub-study 2).

Results

For sub-study 1, 3726 females aged 18 in 2013 were invited to fill a questionnaire on personal demographics and HPV risk factors and to provide a self-collected cervicovaginal sample for HPV genotyping and Chlamydia Trachomatis PCR. Personal data were evaluated by univariable and multivariable statistics. In sub-study 2, the proportion of the vaccine-type HPV among anogenital HPV was examined with archived genotyping data of more than 8050 outpatients participating to cervical cancer screening from 1999 until 2018. The yearly evolution of this proportion was evaluated by segmented logistic regression.

Conclusion

690 (18.5%) women participated to sub-study 1 and 327 (8.8%) provided a self-collected sample. Prevalence of Chlamydia trachomatis (4.6%) and demographics confirmed that the subjects were representative of sexually-active Swiss young women. Vaccine (five-year coverage: 77.5%) was preferentially accepted by contraceptive-pill users (p=0.001) and samples were mainly provided by sexually-active subjects (p<0.001). The proportion (4%) of the vaccine-type HPV in this population was lower than in sub-study 2 outpatients until 2015 (n=849, <26 years old) in the pre-vaccine era (25.7%). The proportion of the high-risk vaccine-type HPV decreased significantly (59%, p=0.0048) in the outpatients during the post-vaccine

era, yet this decrease was restricted to those aged less than 26 years (n=673, p=<0.0001) until 2015 (Jacot-Guillarmod M et al. BMC Infectious Diseases (2017) 17; 790). This was confirmed with the additional dataset encompassing 2016-2018.

References

The low proportion of vaccine-type HPV in 18-year-old females and its rapid decrease in young women participating to cervical cancer screening support the success of HPV vaccination to Switzerland. Our data suggest that cervical cancer screening is now entering a stage of reduced proportion of HPV16 and/or 18 in samples reported positive by cytology, leading to new screening strategies based on primary HPV testing.

00060

LONG-TERM ANTIBODY RESPONSE TO HUMAN PAPILLOMAVIRUS VACCINES: UP TO 12 YEARS FOLLOW-UP IN THE FINNISH MATERNITY COHORT

05. HPV prophylactic vaccines

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Background / Objectives

Most cervical cancers are caused by vaccine-preventable infections with human papillomaviruses (HPV). HPV prophylactic vaccines Gardasil™ and Cervarix™ both contain the major oncogenic HPV types 16 and 18, have been widely used for >10 years and are reported to induce high antibody levels and long-lasting protection. A head-to-head comparison of the antibody responses induced by the two vaccines has been performed only up to 5 years.

Results

About 3,500 Finnish females, who participated in phase III licensure trials of the Gardasil™ and Cervarix™ vaccines, consented to follow-up. Linkage with the Finnish Maternity Cohort found that they had donated >2,500 serum samples up to 12 years later. The most recently donated serum samples of 337 Gardasil™ and 730 Cervarix™ vaccine recipients were retrieved and serum antibody levels were determined using Pseudovirion- Luminex for HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59/68 and 73. To determine the level of a natural infection related antibodies, sera from women from Slovenian cervical screening cohort were analysed. Antibody levels were reported in international units (IU) in case of HPV16 and HPV18 and in-house units for the rest of the HPV types. Avidity of the antibodies in seropositive subject was evaluated using ammonium thiocyanate and reported using avidity index.

Conclusion

Post-vaccination HPV16 and HPV18 antibody levels remained stable and above natural infection-related antibody level for up to 12 years for most vaccine recipients. The median antibody levels were higher among Cervarix™ vaccine recipients in all time-windows from 7 to 12 years post vaccination ($p < 0.0001$). Seropositivity rate was higher in Cervarix™ group for all HPV types except HPV6/11/73 ranging from 1.1 fold (HPV16) to 3.3 fold (HPV45) indicating also existence of vaccine-related cross-protective antibodies. Avidity for HPV16 antibodies was 44% in Cervarix™ group and 30.5% in Gardasil™ group. Avidity for HPV18 antibodies was 33% vs. 28%. Higher avidity index in Gardasil™ group for HPV6 (9.3% vs. 27.6%) and HPV11 (10.9% vs. 34.5%) indicated higher quality of the vaccine induced antibodies compared to naturally derived ones. For other studied HPV types avidity indexes did not differ between vaccines tremendously varying from 4.3% (HPV51) to 19.6% (HPV 68) in case of Gardasil™ and 4% (HPV51) to 16% (HPV73) in case of Cervarix™.

References

The long-term stability of vaccine-induced antibody levels is in accordance with the high long-term protection reported previously. The observed significant differences in the antibody levels induced by the two vaccines imply that continued follow-up to identify possible breakthrough cases and estimation of the minimal protective vaccine-induced levels of serum antibodies is a research priority.

00073

Bivalent HPV Vaccine Effectiveness in a Japanese Population

05. HPV prophylactic vaccines

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Background / Objectives

April 2013, both the bivalent and quadrivalent HPV vaccines were included in the Japanese National Immunization Program. However, only two months later, the Japanese Ministry of Health, Labour, and Welfare suspended proactive recommendations for the HPV vaccine after unconfirmed reports of adverse events. One immediate consequence of the suspension was that vaccination uptake plummeted from over 70% to less than 1% within 12 months. A second consequence was that nonavalent HPV vaccine has not been licensed. We investigated bivalent HPV vaccine effectiveness (VE) against vaccine targeted types HPV 16 and 18 as well as against HPV 31, 45 and 52 those pointed out cross protection type.

Results

This study is a cross-sectional study recruiting women born after April 1993 attending for cervical screening at Niigata prefecture. We asked HPV vaccination status and sexual history (obtained on age at sexual debut, and number of sexual partners) in the questionnaire. We also confirmed HPV vaccination status from municipal records. Residual Pap smear specimens were collected for high-risk HPV (hrHPV) screening and genotyping test. We used Hybrid Capture 2 for hrHPV screening test and MEBGENTM HPV kit for hrHPV genotyping test. Data were analyzed using univariate and multivariate logistic regression analyses. VE was calculated as %VE=100x(1-OR).

Conclusion

The study enrolled a total of 2197 participants and included 1814 in the analysis. Of those analyzed, 1355 women had received the bivalent vaccine confirmed by municipal records. And 459 women were unvaccinated status by serf-reports and municipal records. In the univariate model, VE was statistically significant for pooled HPV 16/18 infections at 89.8%, (95% CI: 63.9% to 97.2%, p=0.001). VE of the women who were sexually naive at HPV vaccine initiation for pooled HPV 16/18 and HPV 31/45/52 was statistically significant at 95.5% (95% CI: 64.6%-99.4, p=0.0001)

and 71.9% (95% CI: 44.4%-85.8%, p=0.0002). VE for HPV 16, 31 and 52 individually was 94.3% (95% CI: 54.8%-99.3%, p=0.0005), 100% (p=0.008) and 63.1% (95% CI: 24.0%-82.1%, p=0.007). VE against HPV 18 and 45 individually was 100%, but did not reach statistical significance, due to the low overall number of infections. Adjusted for number of sexual partners, VE was 91.9% in HPV 16/18 (95% CI: 33.8%-99.0%, p=0.02) and 53.5% in HPV 31/45/52 (95% CI: 2.5%-77.8%, p=0.04).

References

We have shown high VE of the bivalent vaccine against vaccine-targeted hrHPV types 16 and 18 and significant cross protection against pooled hrHPV types 31, 45 and 52, which are associated with an additional 10% of ICC in Japan. This means the bivalent vaccine may be able to prevent around 80% of ICC in Japan. We hope Japanese government will resume proactive recommendations for HPV vaccine immediately.

00087

REDUCTION IN HPV16/18 POSITIVE HIGH-GRADE CERVICAL LESIONS IN A POPULATION OFFERED CATCH-UP VACCINATION

05. HPV prophylactic vaccines

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Background / Objectives

Australia introduced an ongoing, government-funded, school-based quadrivalent [HPV6,11,16,18] HPV vaccination program in 2007 for young girls 12-13 years of age, with a catch-up program to 26 years of age for women to the end of 2009. Using laser capture microdissection (LCM) and sensitive human papillomavirus (HPV) DNA genotyping, this study aimed to determine what impact the vaccination program has had on the proportion of HPV16/18-positive cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) in young women of vaccine-eligible age living in Victoria, Australia, compared with pre-vaccination rates.

Results

Consecutive, histologically-confirmed CIN3 or AIS positive biopsies were collected between May 2011 and December 2014, from vaccine eligible women (born after 30th June 1981). Biopsy specimens were obtained from the Royal Women's Hospital Dysplasia Clinic (Parkville, Victoria, Australia) and VCS Limited (Carlton, Victoria, Australia). HPV genotypes present in whole tissue sections (WTS) were determined by a sensitive reverse hybridisation assay; RHA kit HPV SPF10-LiPA25, version 1 (Labo Bio-medical Products). Where the WTS was positive for multiple genotypes, lesions were isolated from biopsy material using LCM and genotyped. Cervical cytology samples from a pre-vaccine cohort with CIN3/AIS had been previously collected and genotyped using HPV Linear Array HPV Genotyping Test (Roche Diagnostics). Mixed genotype detections in the pre-vaccine sample set were resolved to a single lesion-attributed genotype using hierarchical attribution.

Conclusion

Overall, 743 cases were included. In the 18-25 year old group, the proportion of HPV16/18 cervical high-grade lesions decreased significantly over time from 69.4% in 2001-2005 (pre-vaccine), to 62.2% in 2011-2012, to 47.2% in 2013-2014 (p-trend=0.004). There was no significant change in HPV16/18 in the 26-32 year old group (p-trend=0.147).

References

In vaccine-eligible women aged 18–25 years old at time of biopsy, the proportion of CIN3/AIS lesions attributable to HPV16/18 was significantly lower than in a pre-vaccine-era cohort, giving an early indication that the Australian HPV vaccination program is effectively reducing cervical disease due to HPV16/18 infection.

00115

COMPARABLE VACCINE EFFECTIVENESS AGAINST CERVICAL INTRAEPITHELIAL NEOPLASIA AFTER VACCINATION WITH TWO OR THREE DOSES OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE

05. HPV prophylactic vaccines

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Background / Objectives

Although originally approved for three-doses, HPV vaccines were later approved for a two-dose schedule for 9-14 year olds. Registration of the two-dose schedule was based on immunobridging studies. We aimed to estimate the vaccine effectiveness (VE) of 2- and 3-doses of quadrivalent HPV vaccine (HPVV) against high-grade squamous intraepithelial lesion (HSIL) and cervical intraepithelial neoplasia grade 2 or higher (CIN2+) in screened young women.

Results

Data-linkage was performed between the population-based Cervical Cancer Screening Program (CCSP) and an immunization registry in British Columbia, Canada. Occurrence of HSIL and CIN2+ (CIN2 or CIN3) were compared in a screening cohort of women born between 1994-2005 who were unvaccinated or vaccinated with a recommended 2- or 3-dose schedule between 9-14 years of age

through a publicly funded school-based program. Incidence rates (IR, (95%CI)) and relative rates (RR) were calculated using adjusted Poisson regression. The VE was calculated as 1-RR *100%.

Conclusion

In total 26,059 women were included in our analyses; 12,762 were unvaccinated, 690 received a recommended 2-dose schedule and 12,607 a recommended 3-dose schedule. We observed a significant adjusted vaccine effectiveness (VE) against HSIL among women vaccinated between 9-14 years of age with either a recommended 2 (72.3%, 95CI 24.0-98.4%) or 3-dose schedule (37.7%, 95%CI 20.8-51.1%) compared to unvaccinated women. The IRs for CIN2+ among women vaccinated with two or three doses were 0.26 per 1000 person-years (PY) (95%CI 0.06-0.97) and 0.49 per 1000 PY (95%CI 0.36-0.66) respectively. There was no statistically significant difference in the relative rate of 2- compared with 3-doses for CIN2+ (adjusted RR 0.71 95%CI 0.07-6.66).

References

In this observational study, we did not observe a difference in VE after two-or three-doses of HPVV against both HSIL and CIN2+.

00355

PROTECTIVE EFFICACY OF THE AS04-HUMAN PAPILLOMAVIRUS (HPV)-16/18 VACCINE AGAINST NON-VACCINE HPV TYPES AMONG YOUNG WOMEN WITH CURRENT HPV EXPOSURE: POST-HOC ANALYSIS FROM A RANDOMIZED CONTROLLED TRIAL

05. HPV prophylactic vaccines

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Background / Objectives

HPV vaccines have been proven efficacious against vaccine-type infection among HPV DNA-negative women. It remains unclear whether L1 virus-like-particle-based prophylactic HPV vaccines are efficacious in protecting against high-risk (HR)-HPV types in women HPV DNA-positive for other HPV types at first vaccination.

Results

Women aged 18–25 years from Jiangsu province were randomized (1:1) to receive the AS04-HPV-16/18 vaccine (n=3,026) or $Al(OH)_3$ control (n=3,025) at months 0, 1 and 6 in a phase II/III, double-blind, randomized trial (NCT00779766).[1,2] In this post-hoc analysis, we evaluated the vaccine efficacy (VE) in specific subsets of women DNA positive to certain HR-HPV type(s) (i.e., 16/18/31/33/35/39/45/51/52/56/58/59/66/68) in the total vaccinated cohort. Subjects were included in this analysis if they were DNA negative for the HPV type(s) considered for efficacy and positive for any of other HR-HPV type DNA at baseline.

No initial serostatus was considered, except for analysis on women DNA negative and seropositive for HPV-16/18.

Conclusion

At baseline, DNA positivity was 15.3% for HR-HPV and 12.6% for HR-HPV excluding HPV-16/18. VE against 6-month persistent infection (6MPI) with HPV-16, HPV-18 and HPV-16/18 (any of those) among women DNA negative for HPV-16 and/or HPV-18 at baseline and positive for any other HR-HPV at baseline were 100% (95% confidence interval: 56.6–100%), 100% (18.7–100%) and 100% (75.4–100%), respectively. Similarly high VE (100% [33.1–100%]) against 12-month PI with HPV-16/18 was also observed in this population. In women who cleared prior infection to HPV-16/18 (DNA negative and seropositive to HPV-16/18), VE was 95.5% (72.0–99.9%) against HPV-16/18 6MPI.

We also noted substantial VE at 56.6% (16.2–78.6%) against incident infection associated with non-vaccine types HPV-31/33/45 among women positive for any of the highly prevalent HPV-39/51/52/58/66 and negative for HPV-31/33/35 at baseline. For women DNA positive for HPV-16/18 but negative for HPV-31/33/45 at baseline, efficacy against incident infection due to HPV-31/33/45 was 71.0% (27.3–89.8%).

References

Our findings lend support that for women with current exposure to any HR-HPV types at the time of first vaccination; vaccination with AS04-HPV-16/18 vaccine may protect against HPV infection caused by certain other high-risk oncogenic types. These results support AS04-HPV-16/18 vaccination of the general population without prescreening and vaccination among those with known HR-HPV infection status even for HPV- 16/18.

Funding: GlaxoSmithKline Biologicals SA.

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00550

ONE DOSE OF HUMAN PAPILLOMAVIRUS VACCINE IS AS EFFECTIVE AS THREE FOR PREVENTION OF HIGH-GRADE CERVICAL LESIONS: NATIONAL COHORT STUDY

05. HPV prophylactic vaccines

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Background / Objectives

Prophylactic human papillomavirus (HPV) vaccines are highly effective at preventing pre-cancerous cervical lesions when given in a three-dose schedule. Some post-hoc trial data suggest that one dose prevents HPV infection. If one dose could prevent pre-cancerous cervical lesions, then global cervical cancer prevention would be greatly facilitated. We assessed the effectiveness of quadrivalent HPV vaccine by number of doses against cervical intraepithelial neoplasia (CIN) 2 or 3/adenocarcinoma-in-situ (AIS) in Australia up to seven years post vaccination.

Results

We created a linked dataset containing HPV vaccination history, cervical screening results, vital status and de-identified demographic details for all Australian women aged 15 or under when eligible for vaccine who had a screening test between April 2007 (when vaccination commenced) and 31 December 2014. We used Cox proportional hazard regression, adjusted a priori for age, socioeconomic status, and area of residence, to estimate hazard ratios of histologically confirmed CIN2/CIN3/AIS.

Conclusion

We included 250,648 women: 48,845 (19.5%) unvaccinated, 174,995 (69.8%) had received three doses, 18,190 (7.3%) two doses and 8,618 (3.4%) one dose. The

adjusted hazard ratio was significantly lower and not significantly different between dose groups compared to unvaccinated women (1 dose 0.63 (95%CI 0.51-0.79), 2 doses 0.60 (0.51-0.71) and 3 doses 0.60 (0.55-0.66).)

References

Despite differences in underlying characteristics of partially vaccinated women, we found that one dose was as effective as three at preventing high-grade disease. This finding supports decision makers to include one dose vaccination as a viable strategy when working towards the global elimination of cervical cancer.

FC 12. Vaccines 4

00131

THE HPV SEROLOGY STANDARDIZATION INITIATIVE: AIMS AND PROGRESS TO DATE AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH

05. HPV prophylactic vaccines

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Background / Objectives

Protection against Human Papillomavirus (HPV) infection after vaccination is believed to be mediated by HPV-specific antibodies. Antibody responses in HPV prophylactic vaccine trials have been assessed using different methods. The lack of standardized assays, procedures, and reagents accessible to the scientific community has precluded the comparison of different studies evaluating immunogenicity of HPV vaccines. With an expected increase in the number of trials relying on immunobridging for approval of new dosing schedules or vaccine formulations, there is a critical need for standardized measurement and reporting of immunogenicity to reliably assess non-inferiority of antibody responses and improve overall comparability between studies.

Results

The HPV Serology Laboratory at Frederick National Laboratory for Cancer Research was established in January 2017 to address this challenge, working with the National Cancer Institute (USA) and the Bill & Melinda Gates Foundation to lead standardization and harmonization efforts for HPV serological testing within HPV prophylactic vaccine trials.

The main goal is to expedite serology assay standardization by developing a critical set of qualified immunoassay reagents, including secondary standards and HPV Virus-Like Particles (VLP), as well as validated assays that will be made available to

the HPV scientific community. Furthermore, standard operating procedures for reagent production and qualification methods will be made accessible.

Conclusion

The HPV Serology Laboratory is currently developing qualified HPV VLP for the 9 HPV types included in currently licensed vaccines, HPV antibody secondary standards, serology-based proficiency panels, qualified serology assays, and testing guidelines. This work is being done in partnership with other HPV serology laboratories in the world.

References

Achievement of these aims will enable comparisons of data across different HPV vaccines and different studies and, therefore, it will facilitate vaccine development and implementation of new vaccine indications and new vaccine candidates.

00134

EFFECT OF BIVALENT HPV IMMUNISATION ON CYTOLOGICAL AND HISTOLOGICAL FINDINGS AT SECOND AND SUBSEQUENT SCREENS - A LONGITUDINAL STUDY

05. HPV prophylactic vaccines

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Background / Objectives

Scotland implemented school-based routine hr-HPV immunisation with Cervarix® at age 12/13 for women born in and after 1995, with catch-up immunisation for women born between 1990 and 1995. Women in the catch-up cohort have been screened since 2010, and routinely immunised women since 2015. As eight years have elapsed since the first immunised women began screening, it is possible to document the effect of HPV immunisation at the second and subsequent screening rounds for women in the catch-up cohort. This will be the first longitudinal data on the effect of bivalent HPV immunisation with direct linkage between immunisation and disease outcome

Results

Data on all cytology results and histology results, together with the number of doses of vaccine received, were extracted from the Scottish National Screening database for all women born between 1 January 1988 and 6 June 1996. Women born in 1988-1990 are largely un-immunised, women born in 1991-1994 are the catch-up cohort, and those born in 1995 and 1996 are the routinely immunised cohort. The reporting rates of cytological abnormalities and the histologically confirmed disease rates are compared between immunised and non-immunised women at their second and subsequent attendance for screening.

Conclusion

A total of 409,847 women were identified within the age range. A total of 127,855 women have had more than one cytology result recorded of whom 94,854 had negative cytology at their first screen. The cytology results and histological diagnoses taken from these women three years or more after their initial screen are shown in the table below, categorized by either no immunization or full immunization. Further detail on disease outcomes by birth cohort and time since first screen, stratified by immunisation status will be presented.

		Non immunised n (%)	Fully immunised n (%)
No. of women with negative initial screen		59792	30873
No. of cytology samples taken >=3 years after initial screen		104784	36486
Cytology	Negative	87033 (84.27)	31616 (88.05)
	Low grade	13726 (13.29)	3976 (11.07)
	High grade	2516 (2.44)	315 (0.88)
	? invasive	6 (0.006)	1 (0.003)
Histology	Negative	564 (0.54)	86 (0.24)
	HPV/CIN1	998 (1.30)	138 (0.38)
	HG CIN	2444 (2.34)	248 (0.68)
	Cancer	24 (0.023	2 (0.006)

References

In this analysis of women immunized as part of catchup and followed for up to 9 years, there has been a 64% reduction in the number of cytology samples reported with high grade cytology and a 71% reduction in the number of biopsies reported with high grade CIN. The number of cancers diagnosed is reduced by 75%. Bivalent HPV immunization is providing a substantial level of protection against cervical cancer and precancer that extends into the second round of screening and beyond.

00390

BIVALENT HPV VACCINE EFFECTIVENESS AGAINST ANAL HPV POSITIVITY AMONG FEMALE DUTCH STI CLINIC VISITORS

05. HPV prophylactic vaccines

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Background / Objectives

Anal cancer is responsible for the second largest HPV-related burden among women, with a steadily increasing share of the total disease burden due to rising incidence trends and absence of screening. HPV vaccines hold promise for anal cancer control, but data on vaccine effectiveness (VE) against anal HPV endpoints are scarce, especially among women. We estimated the VE of the bivalent HPV vaccine against type-specific anal HPV positivity among women visiting sexually transmitted infection (STI) clinics.

Results

We selected vaccine-eligible women from the PASSYON study, a biennial cross-sectional study among 16- to 24-year-old STI clinics visitors across the Netherlands. We aimed to include an anal swab of 30% of the women, independent of sexual risk behavior. Swabs were tested using the PCR-based assay SPF10-LiPA25. We compared the anal HPV positivity between self-reported vaccinated (≥1 dose) and unvaccinated women, and estimated the VE by a logistic mixed model against high-risk types HPV16/18/31/33/35/39/45/51/52/56/58/59 and low-risk types HPV6/11.

Conclusion

2246 women had been eligible for HPV vaccination of whom 548 (24.4%) provided an anal swab. Of the 548 women, 46.0% reported ever having had anal sex and 65.1% reported to be HPV vaccinated. Of the vaccinated women 0.8% tested

positive for anal HPV16/18 compared to 7.3% of the unvaccinated women, resulting in an adjusted pooled VE against anal HPV16/18 of 89.9% (63.0%–97.2%); 88.2% against HPV16 and 91.9% against HPV18. Moreover we calculated significant VE against HPV31 (72.9%) and HPV45 (100%).

References

We estimated high VE of the bivalent HPV vaccine against anal HPV16/18 positivity. Because these types are associated with almost 90% of all HPV-related anal cancer cases, vaccination provides a tremendous opportunity for anal cancer prevention.

00460

Impact of state legislation of human papillomavirus vaccination on vaccine uptake in the United States

05. HPV prophylactic vaccines

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Background / Objectives

In the United States, human papillomavirus (HPV) vaccination is universally recommended to adolescents at age 11. However, HPV vaccination rates lag behind those of other recommended adolescent vaccines. We identified states with laws regulating information dissemination or provision of HPV vaccination, and assessed the impact of these laws on rates of HPV vaccine uptake.

Results

The study period was October 2009-December 2014. We identified unvaccinated 11-year-olds adolescents from a commercial insurance claims database, and estimated rates of initiating HPV vaccination for each of 63 months during this period. We then searched the LexusNexus legal database for state laws around HPV vaccination that were passed during this period, and restricted analyses to adolescents in these states. We used segmented linear regression to estimate changes in levels of HPV vaccination (i.e. sudden change in rate), and trends of HPV vaccination (i.e. change in the slope of the rates) after passing the laws in each state. Model covariates included study month, time segment (pre- or post-legislation), time since passage of the legislation (months), and transformed sine and cosine functions of the rates to control for seasonality of vaccination.

Conclusion

Four states passed laws during the study period: Indiana (March 2013), Kentucky (February 2012), Missouri (July 2010), and Oregon (June 2013). Indiana's law allowed pharmacists to administer HPV vaccination. Laws in Kentucky, Missouri, and Oregon mandated education about HPV infection and cervical cancer. Only Oregon had a significant increase in HPV vaccination rates over the entire study period ($\beta=0.0319$, $p<0.0001$); however, rates slightly decreased after the law was passed in June 2013 through December 2014 ($\beta=-0.042$, $p<0.05$). Boys, but not girls, had significant increases in HPV vaccination rates in Indiana, Missouri, and Oregon over the entire study period. Boys in Missouri had significantly higher HPV vaccination rates after the law was passed in July 2010 through December 2014 ($\beta=0.11$, $p<0.05$). Urban adolescents accounted for the changes in HPV vaccination rates in Oregon, as no significant changes were observed in rural adolescents.

References

HPV vaccination rates in these four states did not show significant increases following the passage of pro-vaccination legislation. We saw positive trends among boys in Missouri, but across all states girls and rural adolescents did not have significantly higher vaccination rates after passage of legislation. School vaccination mandates without broad exemptions are needed to estimate their potential impact on HPV vaccination rates.

00465

HPV VACCINE PRESCRIPTION AND COMPLIANCE IN A COHORT OF WOMEN REFERRED FOR COLPOSCOPY

05. HPV prophylactic vaccines

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Background / Objectives

Human Papillomavirus (HPV) is a sine qua non factor for the development of cervical cancer. It is also associated with vulvar, vaginal, anal, oropharyngeal and penile cancer. Portugal introduced HPV vaccination of adolescent girls in 2008; since 2017 the schedule was changed to 2 doses of Gardasil 9 at age 10. Coverage rate of this program is of about 90%. Nevertheless, a significant part of older women are not vaccinated. The Portuguese Society of Gynaecology recommends vaccinating all women≤26 years old, and those with a diagnosis of a high grade cervical intraepithelial neoplasia (HSIL). The purpose of our work was to evaluate the prescription criteria and vaccination compliance in a cohort of women referred for colposcopy.

Results

Retrospective analysis of data from women who had their first appointment with one physician of our cervical pathology unit between January 2014 and July 2017 was performed. Demographic data (age, profession, civil status, immunosuppression, smoking), screening tests results, vaccine status, prescription and compliance were evaluated.

Conclusion

A total of 325 women were included, with ages ranging between 19 and 72 years old (median 40y, IC:32-47). Only 33 (10.2%) had already been immunized anti-HPV. Out of the others, the vaccine was prescribed in 34.9% of cases (n=102). Women with HSIL in histological evaluation were prescribed the vaccine in 51.5% (n=28) of the cases. The bivalent vaccine was prescribed in 79 cases (77.5%), followed by the nonavalent (n=18, 17.6%) and the quadrivalent (n=5, 4.9%). Half of the women (n=51) completed the 3 prescribed doses. Two women completed 2 doses; one only the first dose. In 23.3% (n=17) no dose at all was administered; the remaining 29 (28.4%) were lost to follow-up. Compliance was associated with the vaccine prescribed (bivalent 80.4% vs.tetravalent 50% vs.nonavalent 33.3%, p=0.003).A more severe Pap test

result showed a tendency towards higher compliance(>LSIL vs. ≤LSIL 83.3% Vs 64.6%[p=0.099]). On the other hand, no differences were found according to age, working status, smoking, contraception or indication for excision of the transformation zone.

References

Colposcopy is a good opportunity to promote HPV vaccination. It was recommended to one third of women, but compliance was low (50%). Price seems to be a key factor to explain this low uptake. This can explain why the bivalent vaccine was the more often prescribed and also why compliance was higher in this group. However, since the nonavalent vaccine is available, it is recommended as first option. Lower prices and/or state funding could increase the uptake of HPV vaccines.

00625

14 YEARS OF FOLLOW UP ON THE LONG-TERM EFFECTIVENESS AND IMMUNOGENICITY OF THE QUADRIVALENT HPV VACCINE IN 4 NORDIC COUNTRIES

05. HPV prophylactic vaccines

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Background / Objectives

FUTURE II, the pivotal efficacy study of the qHPV vaccine in young women 16-23 years of age was extended to investigate the long term effectiveness, immunogenicity and safety of the vaccine. Here, we present the end of study results after 14 years of follow up.

Results

During the base study participants received 3 doses of qHPV vaccine or placebo and were followed for ~4 years. Participants in the base study residing in Denmark, Iceland, Norway and Sweden were followed an additional 10 years through national health registries for effectiveness. Following the registry-based identification of all cases of high-grade cervical dysplasia, paraffin-embedded tissue blocks were retrieved and cut for thin-section HPV PCR testing. Slides were also created for pathology diagnosis adjudication. Vaccine effectiveness was estimated by comparing the observed incidence of HPV 16/18-related CIN2 or worse with the historical background incidence rate in an unvaccinated population (estimated by combining historical data from the national registries with survey data). An adapted Poisson Shewhart-based control chart approach for breakthrough disease incidence was used to monitor any waning of vaccine effectiveness. Per-protocol efficacy (PPE) analyses included participants who received 3 doses of qHPV vaccine in the base study and were seronegative and DNA negative for the relevant HPV type(s) prior to vaccination. Serum was collected at Years 5 and 10 of the LTFU study for

immunogenicity assessment. Geometric Mean Titers (GMTs) and % seropositivity to HPV 6/11/16/18 were assessed using cLIA and IgG LIA.

Conclusion

No new cases of the primary endpoint of HPV 16/18- related CIN 2 or worse were observed in the PPE population, which represented 2,121 subjects who contributed a total of 24,099.0 person-years of follow-up. A vaccine effectiveness of 100% was observed for at least 12 years post-vaccination with a trend of continued protection through 14 years post vaccination. There were no new cases of the secondary endpoint of HPV 6, 11, 16, 18-related CIN, vulvar cancer and vaginal cancer. Persistent anti-HPV 6, 11, 16, 18 GMTs were observed through 14 years of follow up, with seropositivity rates at end of study >90% for HPV 6, 11, and 18, and 52% for HPV 18 as assessed by cLIA, and >90% for all 4 HPV types, as assessed by IgG LIA.

References

The qHPV vaccine shows continued protection in women for at least 12 years with a trend of continued protection through 14 years of follow-up, and induces HPV 6, 11, 16, and 18 antibody responses that generally persist through 14 years post vaccination.

36. Public health

00330

PROJECTED IMPACT OF VACCINATION ON THE RISK OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION AND PRECANCEROUS LESION

36. Public health

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Background / Objectives

With the introduction of HPV vaccination, HPV-based screening programs will need optimization in the near future. Population-based data on the impact of vaccination on screening outcomes in the context of HPV-based screening are currently very limited. We predicted the impact of vaccination on five-yearly HPV-based screening on screen-detected HPV infections and CIN3+ under different vaccine scenarios.

Results

We included 21,287 women from a population-based screening trial with 14 years of follow-up (POBASCAM). We calculated cumulative incidences of screen-detected HPV infections and CIN3+, and positive predictive value (PPV) of a positive HPV test for CIN3+. The estimates for CIN3+ were based on a new statistical method linking type-specific HPV infections to type-specific CIN3+ [1]. We re-estimated the cumulative incidences and PPV after applying vaccine efficacy under three scenarios: i) bivalent vaccine, ii) bivalent vaccine with cross-protective efficacy, and iii) nonavalent vaccine. Analyses were performed separately for women aged 29-33 with a prevalent HPV infection at baseline (initial screening round) and women aged 29-58 with an incident HPV infection following a negative HPV test at baseline.

Conclusion

In total, 858 women had an HPV infection, leading to a cumulative incidence of 25.5%, which decreased to 18.9%, 15.2%, and 10.5% under the three different vaccine scenarios, respectively. The cumulative incidence of CIN3+ was 4.0% in absence of vaccination and decreased to 1.3%, 0.66%, and 0.18% under the three different vaccine scenarios, respectively. Amongst prevalent HPV infections, the PPV for CIN3+ decreased from 25.0% in absence of vaccination to 10.2% and 2.4% following bivalent and nonavalent vaccination respectively. Amongst incident HPV infections, the PPV decreased from 9.0% to 5.1% and 1.3%, respectively.

References

In the context of HPV-based screening, substantially lower cumulative incidences of screen-detected HPV infections and precancerous lesions must be expected in vaccinated women compared to unvaccinated. HPV vaccination further reduces screening efficiency reflected by the PPV, stressing the need for a screening program with differential risk of disease, for example by prolonging the screening intervals in vaccinated women.

References

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FC 13. New treatments

00522

EFFICACY OF A CARRAGEENAN-BASED LUBRICANT GEL IN INCREASING CLEARANCE OF HPV INFECTIONS IN WOMEN: INTERIM ANALYSIS OF A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

02. Epidemiology and natural history

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Background / Objectives

Carrageenan has been identified as a potent HPV infection inhibitor in preclinical studies. We aimed to evaluate the efficacy of a carrageenan-based lubricant gel in reducing incidence and prevalence of genital HPV infections among sexually active women.

Results

Between January 2013 and June 2017, 280 women aged 18 years and older were randomly assigned to a carrageenan (n=141) or a placebo (n=139) gel to be self-applied every other day for the first month and prior to and following each intercourse during follow-up. Assessments were done at baseline and at 0.5, 1, 3, 6, 9 and 12 months. Sociodemographic, behavioral and sexual history data were collected using computer-assisted self-administered questionnaires. We used Roche's Linear Array assay to detect and genotype 36 genital HPV types in self-collected vaginal samples. The primary outcome (reported previously) was the incidence of a newly detected infection by an HPV type that was not present at baseline. The second primary outcome was clearance of HPV types observed at baseline. We considered two definitions of clearance: 1 negative result and 2 consecutive negative results. We estimated hazard ratios (HR) and 95% confidence intervals (CI) using univariate Cox

models for the clearance of all HPV types. We used Cox models stratified by HPV types and clustered by participants for the clearance of individual HPV types to accommodate the correlated data structure.

Conclusion

67 (48%) of the 141 participants in the carrageenan and 80 (58%) of the 139 participants in the placebo arm were HPV positive at baseline. Baseline and follow-up characteristics were well balanced between arms for these participants. The median follow-up time was 9.2 months (interquartile range: 2.6-13.2). When considering clearance=1 negative result: 36 (54%) participants in the carrageenan and 34 (43%) participants in the placebo arm became HPV negative during follow-up (HR:1.45; 95% CI:0.90-2.32). When considering clearance=2 negative results: 23 (34%) participants in the carrageenan and 22 (28%) participants in the placebo arm became HPV negative (HR:1.23; 95% CI:0.69-2.21). When considering each HPV type individually, there were 174 infections at baseline in the carrageenan arm and 224, in the placebo arm. When considering clearance=1 negative result: 99 (57%) infections in the carrageenan and 123 (55%) infections in the placebo arm were cleared during follow-up (HR:1.35; 95% CI:0.92-2.00). When considering clearance=2 negative results: 62 (36%) infections in the carrageenan and 88 (39%) infections in the placebo arm were cleared (HR:1.10; 95% CI:0.74-1.63).

References

In our trial’s interim analysis, the use of a carrageenan-based lubricant gel was not associated with a significant increase in clearance of genital HPV infections.

00594

Adjuvant VACcination against HPV in surgical treatment of CINlesions,

06. HPV therapeutic vaccines

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Background / Objectives

ABSTRACT

INTRODUCTION: Human papilloma virus (HPV) causes cervical cancer. HPV vaccination is highly effective in primary prevention. There is less known about a possible effect of secondary prevention in women already infected with HPV. Our study proposes to investigate this efficacy in women with precursors of cervical cancer.

RESEARCH QUESTION:

Does HPV vaccination after Loop Electrosurgical Excision Procedure (LEEP), reduce the recurrence of Cervical Intra-epithelial Neoplasia II-III (CIN) lesions?

HYPOTHESIS

HPV vaccination after LEEP for CIN reduces recurrence.

STUDY DESIGN

Multicenter randomized double blind placebo controlled trial

STUDY POPULATION

Adult female patients with CIN II-III treated with LEEP and no prior vaccination for HPV.

INTERVENTION

HPV-vaccination or placebo after LEEP.

USUAL CARE/COMPARISON

Follow-up at 6 and 24 months after LEEP (HPV and cytology), according to the Dutch guideline.

OUTCOME MEASURES

Primary outcome: CIN II-III at 24 months

Secondary: high risk HPV presence, cytology results, number of re-interventions, cost-effectivity, adverse events and quality of life.

Tertiary outcome measure is efficacy of the vaccination after 5 and 10 yrs. Following completion of the trial, long term outcomes from the national screening program for cervical cancer will be obtained at 5 and 10 years.

SAMPLE SIZE

With a power of 0.8 and a two-sided alpha of 0.050, an estimated incidence of 8%(HPV-vaccine) and 3%(placebo)at 2-year follow-up for recurrence: 646 patients are needed. With 15% loss to follow-up, rounded up, a total of 750 patients has to be included.

DATA ANALYSIS

For the primary and secondary outcomes, the relative risk will be estimated comparing the vaccinated group to the placebo group, with 95% confidence intervals with chi-square or Fisher’s exact test for significance. All analyses will be intention-to-treat.

CURRENT STATUS

299/490

We recieved a grant at ZonMW GGG and expect the study to start on January 1st 2019

Results

This is a reseacrh proposal for a RCT. The trial will start around Janauary 1st 2019

References

A randomized trial for adjuvant vaccination with the nanovalent HPV vaccin in women with primary CIN is proposed.

07. Immunotherapy - Immuno-oncology - New treatments

00326

5% 5-FLUOROURACIL (5FU) TOPICAL THERAPY FOR THE TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) 2/3

07. Immunotherapy - Immuno-oncology - New treatments

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Background / Objectives

U.S. guidelines recommend 6 months observation for young women or surgical procedures for treatment of CIN 2/3.(1) There are no recommendations for medical management. Excisional procedures for cervical dysplasia have risks including adverse obstetrical outcomes. Some patients seek alternative therapies Prior studies of intravaginal 5FU as primary and adjuvant therapy to prevent recurrence of CIN 2/3 have been demonstrated to be effective.(2,3)

Results

This is a retrospective case-series from Jan 2014 to July 2018 of women offered options for management of CIN 2/3. These 25 women chose medical management with intravaginal 5FU (a 16-week course of biweekly self-applied intravaginal 5FU). Follow up included pap smear and colposcopy with biopsy at 6- and 12-months after initial diagnosis.

Conclusion

The majority of women were white (56%), privately insured (76%), and nulligravid (64%). The median age was 28 [22-44] years. All participants had a histologically confirmed CIN 2/3. Reasons for pursuing medical management are outlined in Table

1. In cases of women with severe immunosuppression that precluded surgical treatment, 5FU was prescribed while awaiting improved immune status. All women had follow-up at 6 or 12 months. By 6 months 5 women required surgical management for CIN 2/3 and at 12 months, 2 additional women underwent an excisional procedure. 72% (18/25) avoided surgical therapy within 12 months following CIN 2/3 diagnosis.

Table 1

Reason for 5FU	LEEP alternative, n (%)	14 (56%)
	Previous LEEP Procedure, n (%)	6 (25%)
	LEEP with positive margins, n (%)	3 (13%)
	Comorbidity precluding definitive treatment, n (%)	2 (8%)
Surgical Treatment in the 12 month period	Excisional Procedure, n (%)	6 (24%)
	Cryotherapy, n (%)	1 (4%)

References

Topical therapy with 5-FU may be an acceptable alternative for the treatment of cervical dysplasia in a motivated patient seeking an alternative to excisional procedures.

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00387

DEMETHYLATING TREATMENT INDUCES A DOSE- AND TIME-DEPENDENT REVERSAL OF THE MALIGNANT PHENOTYPE AND ANTI-PROLIFERATIVE EFFECTS IN TWO- AND THREE-DIMENSIONAL HPV TUMOR MODELS

07. Immunotherapy - Immuno-oncology - New treatments

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Background / Objectives

Targeted treatment strategies against HPV-induced precancerous or cancerous lesions are still lacking. Analyses on the molecular biology of HPV-induced (pre-)cancer have revealed hypermethylation of both the host as well as the viral genome itself as a central oncogenic feature during HPV-related carcinogenesis. Specifically, hypermethylation of the HPV E2 binding sites (E2BS) in the upstream regulatory region of the HPV genome abrogates the regulatory function of the E2 protein, which allows uncontrolled overexpression of the HPV E6/E7 oncogenes. In addition, hypermethylation and associated silencing of tumor suppressor genes have been shown to occur in HPV-transformed cells.

Based on those observations we hypothesized that treatment of HPV-transformed lesions with demethylating agents could reverse this aberrant viral and host genome hypermethylation, down-regulate HPV oncogene expression and block uncontrolled proliferation, thereby representing a novel and targeted treatment approach.

Results

Seven HPV-transformed cell lines from the head and neck and the uterine cervix were treated with different concentrations of the demethylating agent 5-aza-2'-deoxycytidine. Dose- and time-dependent effects of the treatment on HPV oncogene

expression, cell proliferation and the induction of cell death and senescence were analyzed by a variety of assays. Three-dimensional (3D) tumor models (spheroids and co-cultures with normal keratinocytes) were generated from HPV-transformed cell lines and assessed for treatment effects. Transcriptome profile was analyzed in all treated cell lines using Illumina bead-chip technology.

Conclusion

A dose- and time-dependent down-regulation of HPV oncogene expression, significantly reduced proliferation and induction of apoptosis as well as cellular senescence was demonstrated in treated cell lines and 3D cultures. Transcriptome analysis revealed significant overexpression of cancer/testis antigens in treated cell lines, which has been associated with enhanced anti-tumoral immune response in previous in vivo studies.

References

Demethylating treatment represents a valuable treatment approach for HPV-induced (pre-)cancer by blocking cellular proliferation and potentially inducing an anti-tumoral immune response.

00521

MICROENVIRONMENT IN VAGINA AS A KEY-PLAYER ON CERVIX: VAGINAL MICROBIOTA COMPOSITION AND PREVALENCE OF HPV

17. Microbiome

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Background / Objectives

The vaginal microbiota has been associated to reproductive health and, more recently correlated with cervical carcinogenesis. The vaginal microbiota may modulate susceptibility to human papillomavirus (HPV) and other co-infections. Therefore, we evaluate the association between these infections and the vaginal microbiota.

Results

We evaluated the vaginal bacterial composition in 111 women from a private hospital, mean age 40.7±11.1 (range: 17-68 years old). Vaginal bacterial composition was characterized by deep sequencing of barcoded 16S rRNA gene fragments (V4) and HPV was identified using the Roche Linear Array® HPV genotyping test. The vaginal microbiota was categorized in community state type (CST). The cervical samples were obtained for cytology, HPV, *Ureaplasma parvum, Ureaplasma Urealyticum, Mycoplasma Genitaliumand Mycoplasma Hominis* detection. The method used for HPV detection and genotyping determination was Polymerase Chain Reaction followed by hybridization. The statistical methods used were Chi-square, ANOVA and binary logistic regression (SPSS v.24). Significance was attributed if $P<0.05$.

Conclusion

The *Ureaplasma parvum* was the microorganism more prevalent (88.8%). For molecular diagnostic tests, the majority of women had a normal cytology (78.7%) and 30.9% presented HPV-positive, being all high risk-HPV types. Nevertheless, 60.6% had HPV-positive among women with abnormal cytology (P<0.001). High risk-HPV-positive women were younger (<33 years old) compared to HPV-negative (P=0.020). The younger women presented abnormal cytology (54.2%) and hrHPV-positive (44.1%) in relation to older women (P<0.05). The vaginal microbiota composition constituted by four CSTs: the majority presented CST I (n=63, 56.8%) and CST IV-B (n=26, 32.4%), followed by 2.7% in CST II and 1.8% in CST III. The CST-IV were more presented in older women (81.4%), although not statistically significant. Indeed, older women had a lower number of copies/mL of *Lactobacillus crispatus* in relation to younger women (P=0.001).

References

These preliminary results revealed that the clearance of virus in younger ages may be preponderant in the future development of cervical injuries. Indeed, the lower predominance of *L. crispatus* in older women may contribute to increased production of proinflammatory cytokines.

00423

THE iKNIFE AND ITS USE FOR THE TREATMENT OF CERVICAL ABNORMALITIES.

19. New technologies

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Background / Objectives

Cervical cancer and its precancerous form cervical intraepithelial neoplasia (CIN) commonly affect women of reproductive age. Fertility-preserving trachelectomy procedures are available, but if the excisional margins are not cancer-free, as is the case in 33% of procedures, these women must undergo a hysterectomy, therefore losing their child-bearing potential. Rapid Evaporative Ionization Mass Spectrometry(REIMS), also known as the iKnife (intelligent Knife), analyzes electrosurgery-generated aerosols, using time-of-flight mass spectrometry to provide real time tissue identification without the need for sample preparation, raising the potential for use as an intraoperative diagnostic technique and improving the surgical and fertility outcome for one third of the women who undergo trachelectomy.We conducted a pilot study showing that REIMS can differentiate between cancerous and healthy cervical tissue thus presenting an innovative technique that could drastically improve fertility-sparing operations.

Results

Cervical biopsies of 89 women were cut using a Covidien diathermy hand-piece. The surgical aerosol produced was transferred into a Waters Xevo G2-S mass-spectrometer. The tissue samples were then stained for histopathological validation. These diagnoses were used in multivariate statistical analysis of mass spectroscopic spectral data, including principal components and linear discriminant analysis performed using Offline Model Builder software. Correct classification rate was checked using leave one patient out cross-validation.

Conclusion

The study showed correct classification with REIMS of almost 98%, with correct identification of cancer tissue of 83.3%, of CIN 100% and of healthy tissue 100%.

References

Frozen section is the current method for intraoperative assessment of margin status at the time of trachelectomy, and the concordance between intraoperative frozen section and final histology has been quoted as 84%, significantly lower than the results of the iKnife. In addition to providing real-time information, thus reducing anaesthetic time, the iKnife has the potential to improve the accuracy of intraoperative margin detection. This could potentially increase success rates of trachelectomy, leading to a truly advanced fertility sparing technique in modern surgery. This principle is also under investigation for use in CIN to be ruled out into the colposcopy clinic.

00529

PHOTODYNAMIC THERAPY FOR HIGH GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA: A NEW POSSIBILITY?

19. New technologies

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Background / Objectives

5 to 22% high grade intraepithelial neoplasia (HCIN) can progress to invasive disease. The accepted HCIN treatment is excision of the transformation zone (ETZ). Photodynamic therapy (PDT)can induce cell death and stimulates local immune response, and may be a HCIN alternative treatment. The objective of this study was to evaluate Thin prep (TP) and PCR for high-risk HPV screening, in patients treated of HCIN (CIN 2) with PDT and ETZ, followed by 24 months.

Results

Controlled and randomized study with 40 women with histological diagnosis of HCIN (CIN 2), who collected TP and PCR, pre and post-treatment and followed up for 24 months. The patients were allocated into 2 groups with 20 women in each. ETZ was performed by loop excision procedure electrode. PDT was performed with the application of Methyl aminolevulinate cream 20% (MAL), 10 hours before the procedure and then, a single phototreatment with a LED tip. TP and PCR were collected pre and post treatment, every six months for 24 months.

Conclusion

The post ETZ follow up (24 months) showed that the TP was negative in 95% patients and PCR remained positive in 15% patients. The PDT group showed TP negative in 85% while 35 % patients remained PCR positive.

References

After 24 months of follow up PDT results resembled the ETZ and could be an alternative for HCIN, although dosimetry adjustment is still required.

00543

TOPICAL THERAPIES FOR TREATMENT OF HPV/CIN2-3

20. Diagnostic procedures / management

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Background / Objectives

High-risk human papillomavirus (hrHPV) infection is a precursor to cervical cancer, the leading cause of gynecologic cancer worldwide. Standard-of-care management for high-grade cervical dysplasia (also known as Cervical Intraepithelial Neoplasia or CIN 2-3) consists of surgical therapy which includes cryotherapy, laser therapy, and excisional procedures within the cervical transformation zone. Excisional options include Loop Electrosurgical Excision Procedures (LEEP) or cold-knife-cone (CKC).

Despite the overall success of excisional treatments and relatively low risk of immediate problems from these procedures, there are long-term side effects to consider, particularly in women of childbearing age. Women who undergo excisional procedures for cervical dysplasia potentially carry a 2 to 3-fold increased risk of preterm delivery compared with women without excision history. Women undergo psychological distress associated with the need for invasive procedures, and there are significant economic burdens associated with HR-HPV related disease. The development of a noninvasive patient-controlled mode of treatment has the potential to lower cost, long-term morbidity, and anxiety for women.

There are currently no medical therapies recommended to promote the clearance of HR-HPV infection or CIN. Cervical cancer is a cancer of economic, social, and educational disparities. A medical therapy option would overcome many of the barriers to the currently recommended surgical therapy – cost, requirement of skilled health provider for performing procedures, geographical barriers, patient fear of painful procedures – that are present in both developed and less-developed nations.This presentation will discuss literature on the efficacy topical therapy for management of HSIL.

FC 14. Methylation 1: From risk to triage

00435

THE PERFORMANCE OF FAM19A4/MIR124-2 METHYLATION ANALYSIS AS A TRIAGE TEST FOR HPV-SCREEN POSITIVE WOMEN AND AS A RULE OUT TEST FOR CERVICAL CANCER

12. Molecular markers

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Background / Objectives

Over the last years, the importance of primary hrHPV-based cervical screening has become clear, which has led to an adjustment of the cervical cancer screening program in various countries. Due to the low specificity of primary hrHPV screening, triage of hrHPV-positive women is essential to maintain a sustainable screening programme. DNA methylation analysis of cancer-related genes is a promising tool to identify hrHPV-positive women with cervical cancer or high-grade cervical intraepithelial neoplasia (CIN) in need of treatment. Host genes FAM19A4 and miR124-2 have been identified as attractive methylation markers and have a high potential for functioning as such a triage test. Furthermore, methylation analysis in small cervical cancer series has shown to detect all cervical carcinomas. A negative methylation test could thereby possibly be used as a rule out test for cervical cancer.

This project aimed to clinically validate the FAM19A4 /miR124-2 methylation analysis for the detection of high-grade CIN and cervical cancer in hrHPV-positive women participating in population-based cervical screening. Secondly, we aimed to evaluate the performance of the FAM19A4 /miR124-2 methylation analysis on a large series of cervical cancer.

Results

Archived HPV-positive cervical scrapes of hrHPV-positive women (age 29–61 years), who were enrolled in the VUSAscreen screening trial (ISRCTN64621295), were tested for FAM19A4/mir124-2 methylation analysis (QIAsure Methylation Test). The clinical performance in terms of sensitivity, specificity, NPV and PPV for CIN3+ was assessed. In addition, the positivity rate of FAM19A4/miR124-2 methylation analysis was determined in a large series of cervical cancer samples (scrapes or biopsies) from over 25 different countries worldwide.

Conclusion

In the screening cohort, the cervical scrapes of 276/979 (28.2%) hrHPV-positive women tested positive for FAM19A4/mir124-2 methylation. Cross-sectional performance of FAM19A4/miR124-2 methylation analysis among these women showed a CIN3+ sensitivity of 72.7% (95% CI: 64.8 - 80.6) at a specificity of 78.2% (95% CI: 75.4 – 80.9). An NPV of 95.2% (95C CI: 93.7 – 96.8) was found with a PPV of 32.3% (95% CI 26.8 – 37.8). In the cancer case series (n=513), a FAM19A4/miR124-2 methylation positivity rate of 98.6% was found.

References

FAM19A4/miR124-2 methylation analysis has a strong performance as a triage test for hrHPV-positive women in detecting CIN3+. Importantly, it detects virtually all cervical cancers and could therefore be used as a rule out test for cervical cancer.

References

Additional contribution.

16. Methylation

00104

DNA Methylation Panel for the Triage of HPV Positive Women in a Primary Screening Population.

16. Methylation

S. Reynolds [1], C. White [1], P. Naik [2], R. O'brien [2], T. Pham [2], R. Ladapo [3], L. Pilkington [2], H. Keegan [2], C. Powles [4], J. Barry O'crowley [2], P. Tewari [1], S. O'toole [5], C. Normand [5], L. Sharp [6], G. Flannelly [7], J. O'leary [1], C. Martin [1]

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Background / Objectives

Triage of HPV positive women is one of the key challenges facing HPV primary screening. Specific second round triage tests to avoid large numbers of unnecessary referrals to colposcopy are required. Host methylation factors have been repeatedly shown to be hypermethylated in cervical cancer/pre-cancer and have the potential to triage HPV positive women at high risk of cervical cancer. This study aims to investigate methylation of a specific panel of three markers [CADM1-M18, MALM1 and hsa-mir124-2] in HPV positive women. This study forms part of a larger CERVIVA HPV Primary Screening Study.

Results

In partnership with CervicalCheck, The National Cervical Screening Programme in Ireland, CERVIVA are undertaking a longitudinal HPV primary screening study evaluating triage strategies for managing HPV-positive primary screening tests. In total, 13,496 women attending for routine screening have been enrolled. HPV testing is performed using the Cobas HPV DNA test. HPV positive samples are tested for a panel of methylation specific biomarkers [CADM1-M18, MAL-M1, hsa-mir-124-2] via

Quantitative Methylation-Specific PCR and a Total Methylation Score (TMS) is calculated. Here we present a validation panel of 184 cervical cytology samples with confirmed histology for defining clinically relevant cut-off points that are being determined through ROC analysis for the detection of CIN3+. Testing of the HPV positive samples from the CERVIVA HPV primary screening study is underway.

Conclusion

The validation panel comprises of HPV positive and histology confirmed CIN1, CIN2, CIN3(n=50, 34, 50) and HPV negative/cytology no abnormality detected (NAD) (n=50). The data shows statistically significant differences in methylation scores for all markers (CAD-M1, MAL-M1, hsa-mir-124-2, and TMS(p=0.015, 0.016, <0.001, <0.001)) between those cases with CIN3 and NAD. Similarly, statistically significant differences were observed for all markers (CAD-M1, MAL-M1, hsa-mir-124-2, and TMS(p= 0.018, 0.018, 0.001, <0.001 respectively)) between cases of CIN3 and CIN1. ROC analysis shows an AUC of 0.910 when CIN 3 is compared to NAD. To date the methylation expression pattern of the three biomarkers has been assessed in 519 HPV positive primary screening cervical smears based on preliminary cut-offs, 36.6%(n=175/477) demonstrate elevated methylation scores. Elevated TMS was identified in 30% (65/218), 30.5% (63/206) and 60% (57/95) of cases with normal, LSIL/ASCUS and HSIL cytology respectively.

References

The Total Methylation Score generated by the combination of the methylation markers CADM1-M18, MALM1, and hsa-mir-124-2 shows promise in differentiating high grade lesions from normal and low grade lesions. Longitudinal follow up will be used to determine the clinical value of hyper-methylation in HPV positive women.

00108

EVALUATION OF A VALIDATED METHYLATION TRIAGE SIGNATURE FOR HUMAN PAPILLOMAVIRUS POSITIVE WOMEN IN THE HPV FOCAL CERVICAL CANCER SCREENING TRIAL

16. Methylation

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Background / Objectives

High-risk human papillomavirus (HPV)-based cervical cancer screening requires triage of HPV positive women to identify those at risk of cervical intraepithelial neoplasia grade 2 (CIN2) or worse, while avoiding over-treatment of women with transient HPV infections. HPV FOCAL is a randomized controlled trial which compared HPV (Intervention Arm) to liquid-based cytology (LBC) (Control Arm) screening for secondary prevention of cervical cancer. We evaluated whether methylation testing using the S5 classifier (based on HPV types 16, 18, 31, 33; and host gene EPB41L3) provides diagnostic triage performance similar to a more complex algorithm relying on cytology and HPV genotyping.

Results

Women aged 25-65 underwent screening. Based on known HPV/cytology results and pathology outcomes, groups of baseline specimens were randomly selected for S5 methylation testing (n=257). Group 1: 104 HPV positive (HPV+), abnormal LBC diagnosis (54 CIN2/3; 50 <CIN2); Group 2: 103 HPV+, normal LBC with HPV persistence at 12 mo. (53 CIN2/3; 50 <CIN2); Group 3: 50 HPV+, normal LBC with HPV clearance at 12 mo. (assumed <CIN2). Baseline specimens from eight women who developed invasive cervical cancers during or after the trial were also tested; these were not included in Groups 1-3. For Groups 1-3 combined, the S5 risk scores were calculated and the CIN2/3 relative sensitivity, specificity, and positive predictive value (PPV) were compared with other triage approaches. The methylation testing laboratory was blinded to HPV, LBC and histopathology results.

Conclusion

The S5 risk score showed a highly significant increasing trend with disease severity and HPV viral load. For CIN3, S5 relative sensitivity and specificity were: 93.2% (95%CI: 81.4-98.0) and 41.8% (35.2-48.8), compared to 86.4% (75.0-95.7) and 49.8% (43.1-56.6) respectively for combined abnormal LBC/HPV16/18 positivity (differences not significant); PPVs were 24.8% (18.3-31.5) and 26.2% (18.9-33.3) respectively. S5 was positive in baseline specimens from all eight women with cancers.

References

The S5 methylation risk score had high sensitivity and PPV for CIN3, surpassing US and European thresholds for colposcopy referral. S5 methylation signatures can identify most HPV positive women at increased risk of cervical cancer from their baseline screening specimens.

00150

METHYLATION BIOMARKERS FOR TRIAGE OF WOMEN BELOW THE AGE OF 30 WITH HPV POSITIVE SUREPATH COLLECTED SAMPLES.

16. Methylation

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Background / Objectives

Women below the age of 30 have a higher prevalence of oncogenic human papillomavirus (HPV) than older women, and implementation of primary HPV cervical cancer screening in this age group of women is challenged by the high HPV prevalence. Effective triage methods are therefore required to identify those with high risk of cervical high-grade intraepithelial neoplasia (CIN) and cancer, but equally importantly, to deselect HPV-positive women who are at low risk and can be safely referred for new testing at a later point in time. Here, we evaluate the QIAsure Methylation Test measuring the human biomarkers FAM19A4 and mir124-2, either or not in combination with oncogenic HPV genotyping, as a new potential triage method.

Results

Residual SurePath samples were collected from a population of 429 women positive for oncogenic HPV and cytology ≥ASCUS (age 15-29, average: 25 years). HPV testing was performed using the Onclarity HPV test (BD Diagnostics, Sparks, MD). Samples were reflex tested using the QIAsure Methylation Test (Qiagen, Hilden, Germany). All molecular testing was performed in concordance with manufacturer's specification. Women were referred to follow-up in concordance with Danish Guidelines. In total, 235 out of 429 included women had histology registered in the Danish Pathology Databank within 105-205 days (average 157 days).

Conclusion

A total of 163 women (38%) were hypermethylation positive using the QIAsure Methylation Test. Among the 235 women with histological follow-up, 72 had CIN1, 42 CIN2, 67 CIN3, and 54 had normal histology. When considering HPV and

methylation combined, the sensitivity was 70.1%, specificity 64.9%, PPV 44.3% and NPV 84.5% for ≥CIN3. Women with HPV 16,18,31,33&52 infections have been shown to have a higher risk of developing ≥CIN3 (data from Denmark), thus we considered the HPV genotype information with the methylation status as alternative triage strategy. The results showed a PPV and NPV of 54.2% and 62.1% respectively for the HPV16,18,31,33&52 group. For the NON(16,18,31,33,52) group the PPV and NPV were 8.7% and 97.7% respectively.

References

The resulting sensitivity, specificity, PPV and NPV of QIAsure Methylation Test indicates that this assay is an effective molecular reflex method for oncogenic HPV positive SurePath collected cervical samples from women below the age of 30, both alone and when combined with HPV genotype information. QIAsure Methylation Test can be considered as part of a unified molecular workflow for future molecular cervical cancer screening, saving laboratories the work load of reflex cytology on all oncogenic HPV positive screening samples.

00163

METHYLATION ANALYSIS OF HOST CELL GENES IN FIRST-VOID URINE TO DETECT CERVICAL PRECANCER LESIONS IN A REFERRAL POPULATION

16. Methylation

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Background / Objectives

Methylation of host cell and viral genes in urine has shown potential feasibility for cervical cancer triage and screening. As first-void urine (FVU) already ensures good high-risk (hr)HPV DNA agreement with paired cervical samples (CS), it offers the ability to test both primary hrHPV DNA and methylation markers in the same sample (one-step triage). Furthermore, due to its high preference, non-invasive character, and easy implementation, FVU-sampling is particularly interesting to reach non-participants in current screening programs. Hereto, in this study we report on hrHPV DNA prevalence and accuracy of host cell methylation markers in FVU.

Results

Paired FVU (Colli-Pee®, Novosanis) and CS (Cervex-Brush®, Rovers Medical Devices) were collected from 25- to 64-year-old women who were referred for colposcopy (NCT02714127) at the University Hospital Antwerp (UZA, Belgium). Cytology (ThinPrep® Pap Test, Hologic) and histology were investigated at UZA, followed by HPV DNA type-specific qPCR (AML, Belgium) on paired UCM (UAntwerp, Belgium)-buffered FVU and in PreservCyt® (Hologic) collected CS. Bisulphite converted DNA-extracts of UCM-buffered FVU were analysed for six methylation markers by quantitative methylation-specific PCR (Amsterdam UMC, The Netherlands). Statistics was performed using JMP Pro 13.

Conclusion

Ninety-five women (median 33 years; IQR: 29-43) were included, from whom 87 paired FVU and cervical HPV DNA results were available. A good hrHPV DNA agreement was observed between paired samples (Kappa: 0.62; 95% CI: 0.44-0.80), with a hrHPV DNA prevalence of 74 and 68% in FVU and CS, respectively. In FVU significant differences in host cell methylation levels were observed between high- and low-grade cervical abnormality based on cytology (4/6 genes), colposcopy (1/6 genes), and histological outcomes (2/6 genes) (Mann Witney U-test, $p<0.05$). Receiver operating curve (ROC)-analysis for the six methylation markers according to cytology (HSIL+), colposcopy (high-grade abnormality), and histology (CIN2+ and CIN3) showed a maximum area under the curve (AUC) of 0.73, 0.72, 0.72, and 0.86, respectively.

References

In FVU significant differences in host cell methylation levels were observed between high- and low-grade cervical abnormalities, as well as AUC's between 0.72-0.86 for at least one methylation marker (according to HSIL+/CIN2+/CIN3). Together with the good hrHPV DNA agreement between paired FVU and CS, these findings support the assertion that methylation analysis of host cell genes is feasible in FVU and holds promise as a molecular biomarker panel suitable for one-step triage. However, further study is ongoing and required to evaluate its clinical accuracy.

00170

HPV E4 EXPRESSION AND DNA HYPERMETHYLATION OF CADM1, MAL, AND MIR124-2 GENES IN CERVICAL CANCER AND PRECURSOR LESIONS

16. Methylation

M. Van Zummeren [1], W.W. Kremer [1], A. Leeman [2], M. Bleeker [1], D. Jenkins [2], M. Van De Sandt [2], J. Doorbar [3], D. Heideman [1], R. Steenbergen [1], P. Snijders [1], G.G. Kenter [4], W. Quint [2], J. Berkhof [5], C. Meijer [1]

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Background / Objectives

In this study we evaluate the expression of Human Papillomavirus (HPV) E4 protein (marker for the onset of a productive infection) and hypermethylation of host cell *CADM1*, *MAL*, and *miR124-2* genes (marker for an advanced, transforming infection) in cervical intraepithelial neoplasia (CIN) and cancer.

Results

One-hundred-fifteen cervical lesions were categorized by three pathologists into no dysplasia, CIN1, CIN2, CIN3 or cancer by classical histomorphological grading criteria, and by an immunoscore (cumulative value 0-6) grading system based on Ki-67 (score 0-3) and $p16^{ink4a}$ (score 0-3) expression. Lesions were immunostained for E4 protein and analyzed for hypermethylation of *CADM1*, *MAL*, or *miR124-2* genes. Expression of E4 and hypermethylation levels were related to CIN grade based on both classical and immunoscore grading.

Conclusion

Hypermethylation increased with severity of the lesion as defined by both classical histomorphological grading and immunoscore criteria, and was always present in

carcinomas (22/22). Extensive E4 expression decreased with increasing CIN grade and immunoscore, being most frequent in classically graded CIN1 or in lesions with cumulative immunoscore 1-3 and absent in carcinomas. High-grade lesions (CIN2/3 or immunoscore 4-6) showed less E4 expression, which was inversely related to an increasing hypermethylation. Extensive E4 expression, as observed in a small proportion of high-grade lesions (6/49 and 8/43 respectively), was mostly associated with a negative methylation marker status (5/6 and 7/8 respectively).

References

Our results illustrate the gradual transition of productive CIN (reflected by extensive E4 expression), to advanced transforming CIN (reflected by extensive hypermethylation) and cancer. Expression patterns of E4 and hypermethylation status of host cell genes, may be used to identify cervical lesions at risk for cervical cancer, providing a better guidance for clinicians on treatment decisions.

00215

DNA METHYLATION ANALYSIS IN URINE TO DETECT CERVICAL CANCER AND PRECANCER

16. Methylation

R. Van Den Helder [1], N.E. Van Trommel [1], A.P. Van Splunter [2], B.C. Snoek [2], D.A. Heideman [2], M.C. Bleeker [2], R.D. Steenbergen [2]

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Background / Objectives

Urine samples provide a potential alternative to physician-taken or self-collected cervical samples for cervical screening and is expected to increase the uptake of cervical screening programs. Various studies have shown the feasibility of hrHPV DNA testing on urine. However, screening by primary hrHPV DNA testing requires triage testing, for example DNA methylation analysis, to identify women in need of referral. We recently studied the feasibility of hrHPV DNA testing and host cell DNA methylation analysis in urine for detection of cervical cancer. Secondly, we initiated a clinical study (SOLUTION) to assess the performance of hrHPV DNA and DNA methylation analysis in urine samples for detection of CIN2/3 and cervical cancer using cervical samples as a reference.

Results

Urine samples and paired cervical scrapes were collected from 40 patients with cervical cancer patients and 44 female controls (feasibility study) and tested for hrHPV DNA presence and/or 6 previously identified methylation markers for cervical cancer. In the SOLUTION study, urine, cervical scrapes and/or self-collected cervico-vaginal specimens from 110 CIN2/3 patients and from 110 cervical cancer patients are collected and tested for hrHPV DNA and methylation markers.

Conclusion

Our feasibility study on cervical cancer patients showed a strong to near-perfect agreement between hrHPV DNA testing on urine and cervical scrapes (kappa=0.81). Also, DNA methylation levels in urine were moderately to strongly correlated to those

detected in cervical scrapes of the same patients (Spearman correlation coefficient 0.508 to 0.717). All 6 methylation markers were significantly increased in urine samples of cervical cancer patients compared to controls and revealed a good discriminatory power for cervical cancer in urine (AUC 0.74 to 0.89). SOLUTION study sample collection is currently ongoing and data on the performance of urine-based hrHPV DNA and DNA methylation analysis in comparison with cervical scrapes and cervico-vaginal samples will be presented.

References

Our studies indicate that urine-based hrHPV DNA and DNA methylation testing provides a promising strategy for the early detection of cervical cancer.

00280

DIFFERENTIATING CERVICAL PRE-CANCER FROM INVASIVE CANCER WITH THE S5 DNA METHYLATION CLASSIFIER

16. Methylation

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Background / Objectives

Background: Persistent infection with high-risk human papillomavirus (hr-HPV) is an important co-factor in cervical cancer development and is associated with DNA methylation on both human and viral genes. The S5 DNA methylation classifier, based on target CpG sites of the human gene EPB41L3, and viral late gene regions of HPV16, HPV18, HPV31 and HPV33 (Lorincz A et al., 2016) has demonstrated better performance for detection of CIN2/3 women than either HPV16/18 genotyping, cytology or combination. We tested the performance of S5 in detecting invasive cancers versus pre-cancers and quantified the degree of separation between normal/CIN1, CIN2/3 and invasive cancer S5 scores.

Results

Methods: Methylation status of the S5 selected CpG sites was tested in DNA extracted from formalin-fixed biopsies from the Scottish HPV Archive (UK, n=24) and PreservCyt collected exfoliated cervical cell samples from the Scottish HPV Archive (UK, n=48) and the International Agency for Research on Cancer (Spain, n=100). Samples were histologically defined as negative/CIN1 (n=33), CIN2/3 (n=65) and invasive cancer (n=74). DNA bisulfite conversion was carried out and followed by pyrosequencing for the 6 components of S5. Average methylation was calculated for each marker to define the S5 score.

Conclusion

Results: Methylation at all sites increased proportionally with disease severity with a Cuzick trend value of z = 9.2933 ($p < 2.2x10-16$). The separation of normal/CIN1 from CIN2/3 and from cancer was highly significant (Mann Whitney test, both $p < 0.0001$). S5 also showed highly significant difference between CIN2/3 and invasive

cancer from both IARC-Spain ($p < 0.0001$) and Scottish ($p < 0.003$) cohorts. Receiver operating characteristic (ROC) curves were used to assess the diagnostic potential of S5 in differentiating cancers from CIN2/3. The area under the ROC curve (AUC) was 0.86 (CI 95%: 0.7965 to 0.9131, $p < 0.0001$) with a sensitivity of 79.8% and a specificity of 83.1%, based on a cut-off at highest Youden J index.

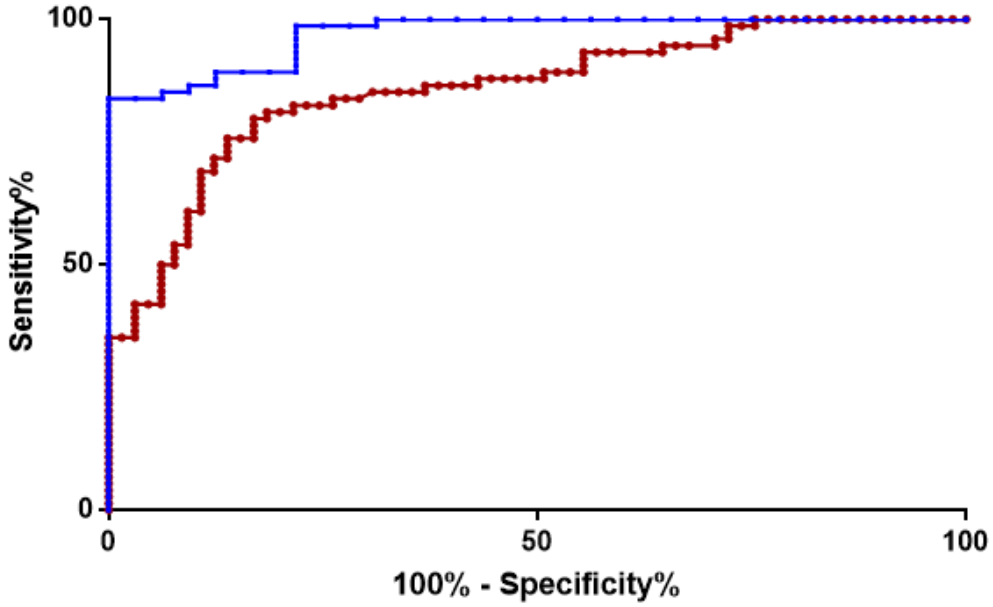
References

Conclusion: The S5 methylation classifier may be useful in cervical screening programs for differentiating pre-cancers from invasive cervical cancers in women infected with hr-HPV. Although the separation was very good, there is room for improvement in S5 by addition of new markers derived from an ongoing multi-omics study using next-Generation Sequencing.

References

Lorincz, A. T. et al. Validation of a DNA methylation HPV triage classifier in a screening sample. Int. J. cancer 138, 2745–51 (2016).

S5 methylation classifier performance ROC curves:
Normal/CIN1 vs Invasive Cancer (blue) and CIN2/3 vs Invasive Cancer (red)



Normal/CIN1 vs. Invasive Cancer
AUC = 0.9696
CI 95% (0.9433 to 0.9959)
p <= 0.0001
Sensitivity = 83.78%
Specificity = 100%
J derived-cutoff = 10.26

CIN2/3 vs Invasive Cancer
AUC = 0.8579
CI 95% (0.7965 to 0.9193)
p <= 0.0001
Sensitivity = 79.73%
Specificity = 83.08%
J derived-cutoff = 13.68

00334

FAM19A4/MIR124-2 METHYLATION ANALYSIS IN THE POBASCAM TRIAL WITH LONG-TERM FOLLOW-UP

16. Methylation

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Background / Objectives

DNA methylation analysis of HPV-positive cervical scrapes using *FAM19A4* and *miR124-2* genes has shown a good clinical performance in detecting cervical cancer and advanced CIN lesions in need of treatment. This study was conducted to assess the performance of *FAM19A4/miR124-2* methylation analysis in an HPV-positive screening cohort with long-term follow-up.

Results

Archived HPV-positive cervical scrapes of 1,040 women (age 29–61 years), who were enrolled in the POBASCAM screening trial (ISRCTN20781131) were tested for *FAM19A4/miR124-2* methylation. The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), was consulted to complete cytology and histology follow-up results over 14 years, comprising three screens (baseline, and after 5 and 10 years) .

Conclusion

The baseline scrape of 36.1% (n = 375) women tested positive for *FAM19A4/miR124-2* methylation and 30.6% (n = 318) had abnormal cytology (threshold borderline dyskaryosis or ASCUS). Within screening round capability of *FAM19A4/miR124-2* methylation to detect cervical cancer was 100% (11/11, 95% CI: 71.5–100). Kaplan–Meier estimate of 14-year cumulative cervical cancer incidence was 1.7% (95% CI: 0.66–3.0) among baseline methylation-negative and 2.4% (95% CI: 1.4–3.6) among baseline cytology-negative women (risk difference: 0.71% [95% CI: 0.16–1.4]). Results on the performance of *FAM19A4/miR-124-2* methylation analysis for CIN3+/2+ is currently ongoing and these data will be presented.

References

A negative *FAM19A4/miR124-2* methylation test provides a low cervical cancer risk in HPV-positive women of 30 years and older. *FAM19A4/miR124-2* methylation testing merits consideration as an objective triage test in HPV-based cervical screening programs.

References

Strooper LMA, Berkhof J, Steenbergen RDM, et al. (2018) 'Cervical cancer risk in HPV-positive women after a negative FAM19A4/mir124-2 methylation test: A post hoc analysis in the POBASCAM trial with 14 year follow-up', *Int J Cancer,* [Epub ahead of print]

00377

METHYLATION CAN PREDICT PROGRESSION OF CIN2

16. Methylation

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Background / Objectives

A substantial number of cervical cancer precursors, cervical intraepithelial neoplasias (CIN), regress without intervention. To date there is no method to predict their outcome, leaving treatment dependent on repeated examinations. A prognostic test could change the outline of cervical cancer screening and treatment of CIN. We investigated the ability of a DNA-methylation panel (the S5-classifier, composed of tumour suppressor gene EPB41L3 and HPV-targets) to discriminate between progression and regression among women with untreated CIN grade 2 (CIN2).

Results

Pyrosequencing methylation assays were run on exfoliated cervical cells from 149 women in a cohort study of active surveillance of CIN2 for 2 years in 18-30-year-old women in Helsinki University Hospital, Finland (ISRCTN91953024).

Conclusion

Twenty-five lesions progressed to ≥CIN3, 88 regressed to <CIN1, and 36 lesions persisted (CIN1/2). When cytology, HPV16/18-genotyping, and S5 at first visit were compared to clinical outcomes, S5 was the only marker associated with progression, odds ratio of 3.39 (95% confidence interval (CI) 1.35-8.50). S5 also showed significantly increased sensitivity compared to cytology in the outcome comparison of regression vs. persistence/progression. With both tests set at a specificity of 38.6% (95%CI 28.4-49.6) the sensitivities were 83.6% (95%CI 71.9-91.8) for S5 and 62.3% (95%CI 49.0-74.4) for cytology high grade squamous intraepithelial lesion (HSIL) (p=0.005). The highest area under the curve (AUC) was 0.735 (95%CI 0.621-0.849) achieved in the regression vs. progression outcome group with a combination of S5

and cytology ≥HSIL, whereas HPV16/18-genotyping did not provide additional prognostic information.

References

S5 classifier alone shows high potential as a prognostic biomarker to identify women with progressive cervical disease. S5 in combination with cytology ≥HSIL could be a useful triage test for women with CIN2 at risk of progression.

FC 15. Self-sampling 1

00064

FOR HIGH-RISK HPV TESTING THE SENSITIVITY AND SPECIFICITY OF A URINE SAMPLE EQUALS THAT OF A SELF-COLLECTED VAGINAL SAMPLE

10. Self-sampling

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Background / Objectives

Increasing focus has been added toward self-collected vaginal (SCV) samples as a means to increase the participation in the screening program for cervical cancer. Urine samples have also been tested for this purpose, but the knowledge on performance is still quite sparse.

The objective of this study is to:

in a colposcopic setting to examine the clinical performance of a self-collected sample (Evalyn Brush) from vagina (SCVS) and a urine sample compared to a sample taken by a physician for detecting high-grade pre-cancer lesions on cervix.

Results

Women referred to colposcopy at the gynecological departments at Lillebaelt Hospital and Odense University Hospital is being invited to participate in the study. Until now 270 women have been enrolled.

A urine sample and SCVS are performed by the women after a short instruction and before the medical examination. At the colposcopy an LBC sample (ThinPrep) and biopsies are taken. The urine, SCVS and LBC samples are analyzed for the presence of high-risk HPV using the Cobas HPV test, Roche. The biopsies are stained with H&E and p16 and are evaluated by gyneco-pathologists and used as the gold standard for the study.

Conclusion

The concordance between SCVS-urine and SCVS-LBC was high: 91% for both, while for urine-LBC it was 81%. For the sensitivity we found no significant differences: at CIN2+ it was 96%, 95% and 94% for SCVS, urine and LBC, respectively. At CIN3+ the values were very high: 100%, 100% and 97%, respectively.

Regarding specificity for SCVS, urine and LBC, at CIN2+ we found 42%, 45% and 44%, respectively and at CIN3+ 38%, 42% and 40%, respectively.

Among the women one carcinoma were identified and for this patient all three samples were positive for high-risk HPV positive.

References

These present data indicate that both the sensitivity and specificity of a urine sample equals that of a SCVS and the physician-taken LBC sample to identify CIN2+ cases. Updated data will be presented.

00213

PRIMARY HPV-BASED SCREENING WITH THE COBAS® HPV TEST ON SELF-COLLECTED CERVICOVAGINAL SAMPLES FROM UNDERSERVED GREEK WOMEN. PRELIMINARY RESULTS OF THE GRECOSELF STUDY.

10. Self-sampling

K. Chatzistamatiou [1], A. Tsertanidou [2], E. Mouchtaropoulou [3], K. Pasentzis [3], T. Moysiadis [3], A. Skenderi [4], S. Angelidou [5], E. Katsiki [5], V. Moschaki [6], A.M. Kaufmann [7], K. Stamatopoulos [3], T. Agorastos [2], S.G. Grecoself [2]

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Background / Objectives

To assess the performance of HPV-based cervical cancer screening in underserved Greek women using the cobas® HPV Test on self-collected cervicovaginal samples, compared with historical real-life results of cytology-based screening.

Results

The GRECOSELF project involved recruitment of women between 25-60 years old who do or do not attend cervical cancer screening and reside in rural areas of Greece. Sample size has been calculated at 12,700 women who would be enrolled over a period of 30 months starting May 2016. Women are contacted by midwifes, who comprise a nationwide network organized for the study purposes, at their place of residence, and are provided, after giving their written informed consent, with a self-sampling kit along with the necessary instructions. Each woman collects the specimen and fills in a questionnaire designed to give information about her cervical screening participation and outcome history, and the acceptance of the self-sampling

procedure. Samples are tested using the cobas® HPV Test, Roche®, which detects HPVs 16 and 18 separately, and HPVs 31,33,35,39,45,51,52,56,58,59,66 and 68 as a pooled result. Women found positive for HPV are referred for colposcopy. Prior to colposcopy a physician-collected sample is taken to be tested for Cytology and Multiplex Genotyping (MPG). In case of abnormal colposcopic impression biopsies are taken. If biopsy is normal the woman is referred to routine screening, if there is Cervical Intraepithelial Neoplasia (CIN) grade 1 or 2 or worse (CIN2+) she is referred to follow up or appropriate treatment respectively.

Conclusion

Between May 2016 and June 2018 12,758 samples were collected and 12,262 were tested (12,066 with valid results), of which 1008 (8.35%) were hrHPV positive and 168 (1.39%) were HPV 16/18 positive. To date, 702 colposcopies have been performed. Low grade disease (CIN1) was histologically detected in 67 cases, whereas high-grade disease (CIN2/CIN3/AIS) was diagnosed in 68 cases. Moreover, there had been two cases of Vaginal Intraepithelial Neoplasia (VaIN) and one case of invasive cervical adenocarcinoma. The prevalence of high-grade disease or cancer was 10.1% among the women referred to colposcopy. According to the historical data of the 71 women detected with CIN2/CIN3/AIS or cancer, 54 had a Pap test during the last three years (abnormal in only 5 cases), 12 before the last three years, and 5 did not have a Pap test in the past. The women with invasive adenocarcinoma reported a “normal” smear test during the last 3 years.

References

The preliminary report of the GRECOSELF study shows that HPV DNA testing with partial genotyping on self-collected cervicovaginal samples is a feasible and more effective than cytology cervical cancer prevention method for Greek women residing in rural areas.

00214

CERVICOVAGINAL SELF SAMPLING ACCEPTANCE AMONG UNDERSERVED GREEK WOMEN. A SURVEY CONDUCTED WITHIN THE FRAMEWORK OF THE GRECOSELF STUDY.

10. Self-sampling

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Background / Objectives

To assess the acceptance of cervicovaginal self-sampling using the Roche® self-collection device among Greek women residing in rural areas within the framework of the GRECOSELF project.

Results

Women recruited within the framework of the GRECOSELF project are between 25-60 years old, with different attitudes towards cervical cancer screening and reside in rural areas of Greece. Women are contacted by midwifes, comprising a nationwide network organized for the study purposes, at their place of residence, and are provided, after giving their written informed consent, with a self-sampling kit along with the necessary instructions. Each woman collects the specimen and fills in a questionnaire. Women positive for HPV are referred for colposcopy. The questionnaire is specifically designed to investigate cervical screening participation and outcome history, and self-sampling acceptance. The questions related to the latter were as follows: 1) “Did you understand the instructions given?”, 2) “Did you experience difficulties during self-sampling?”, 3) “Did you feel uncomfortable during self-sampling?” 4) “Did you feel pain during self-sampling?”, 5) “How sure are you that you followed the instructions correctly?” 6) “If self-sampling was an option where would you prefer to do it?”, 7) “Have you ever felt uncomfortable during physician-

sampling?” 8) “If physician and self-sampling were equally effective which one would you prefer?”, 9) “If physician and self-sampling were equally effective, would you check yourself more often?”

Conclusion

Between May 2016 and June 2018 12,758 women were recruited and 10,905 questionnaires were processed (85.5%). Most of the women (92.2%) stated that the self-sampling instructions were very clear or clear and 88.5% reported having very few or a few difficulties during self-sampling. Regarding discomfort and pain, most women reported having none of these (80.9% and 86.6% respectively). Moreover, 70,9% of the women felt very confident that they had followed the instructions correctly, and 61.8% reported that they would prefer to self-sample at home. A 34% of the women recruited stated that they had felt somehow or very uncomfortable during physician-sampling in the past. Concerning sampling preference, 64.7% of the women preferred self-sampling, 10.0% preferred physician-sampling and 19.4% had no preference. Finally, 68.9% of the women reported that they would be examined more often if self-sampling was equally effective to physician-sampling.

References

The survey conducted within the GRECOSELF study, regarding the acceptance of the self-sampling process in Greek women residing in rural areas showed that self-sampling is the preferred method, compared to physician-sampling, is easy to perform and causes minimal discomfort to women.

00323

EVALUATION OF BD ONCLARITY™ HPV ASSAY PERFORMED ON SELF-COLLECTED VAGINAL AND FIRST-VOID URINE SAMPLES AS COMPARED TO CLINICIAN-COLLECTED CERVICAL SAMPLES.

10. Self-sampling

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Background / Objectives

HPV testing conducted on self-samples has already been adopted by some countries to improve participation of hard-to-reach women to cervical-cancer screening programs. Indeed, the use of self-sampling may allow to overcome many social and cultural barriers that hinder women's participation to screening programs[1]. However, accuracy of testing self-samples as compared to clinician-collected samples needs to be evaluated using commercially available PCR-based clinically validated HPV detection kits[2]. The objective of this study was to evaluate BD Onclarity™ HPV Assay on testing vaginal and first-void urine samples as compared to clinician-collected cervical samples (gold standard).

Results

Clinician administered cervical and self-collected vaginal samples, using L-shape Endo/Esocervical and self-vaginal FLOQSwabs™ (Copan), and first-void urine samples, using Colli-Pee (Novosanis), are being collected from women referred to colposcopy for a recent history of cervical dysplasia, attending the Gynaecology Outpatients Clinic of San Gerardo Hospital (Monza, Italy). HPV detection is carried out using BD Onclarity™ HPV Assay on the fully-automated BD Viper™ LT System, able to detect 14 high-risk HPV (hrHPV) genotypes, according to manufacture's instructions. Sample cellularity is also evaluated using an "in house" quantitative real-time PCR detecting the human CCR5 gene.

Conclusion

Promising preliminary results have been obtained from the analysis of samples collected from the first 29 enrolled women. Concordant HPV detection for at least one hrHPV type has been demonstrated in 100% of vaginal self-collected and in 97% of urine samples as compared to clinician-collected samples. HPV16 resulted the most frequently hrHPV type detected followed by HPV31. Infections with multiple HPV types were shown in 38%, 27% and 24% of urine, cervical and vaginal samples, respectively. The majority of samples were found to have an adequate cellularity for all three specimens' types (mean values for urine, vaginal and cervical samples: 1.95E+06, 1.49E+06 and 3.43E+06 cells/sample, respectively).

References

HPV detection in self and clinician-collected samples showed a high degree of concordance using Copan's L-shape Endo/Esocervical and self-vaginal FLOQSwabs™ as well as Novosanis' Colli-Pee device with BD Onclarity™ HPV Assay. Although more studies are necessary to define the accuracy of HPV-testing on self-collected samples, these preliminary data demonstrate promising results for the use of HPV detection by PCR-based molecular methods on vaginal and first-void urine self-collected samples in cervical cancer screening programs.

References

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00327

OPTIMIZING A PROTOCOL FOR THE EVOLUTION OF VAGINAL SELF-COLLECTED SAMPLES USING COPAN FLOQSWAB© DEVICE FOR HPV DETECTION.

10. Self-sampling

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Background / Objectives

Vaginal self-collection samples for STI and HPV screening has been reported in publications since the year 2000, and its use has been advocated to improve women's participation to HPV screening programs. Devices, such as Copan FLOQSwab© (FS), Rovers Medical Evalyn®Brush and Eve Medical HerSwab, are available for self-collected samples. These are transported dry to the laboratory requiring elution in medium prior to testing. The elution procedure used for STI molecular testing usually follows manufacturers' specifications, while for HPV molecular assays different volumes such as 1, 2, 4, 4.6, 5,10 and 20 ml of SurePath or PreservCyt have been used for eluting self-collected samples. The objective of this study was to optimize the medium volume to elute FS vaginal self-samples, transported dry, for the detection of HPV with molecular assays as compared to professional cervical collection.

Results

Self-collected vaginal samples (SCVS) and physician administered cervical samples (PACS) were collected from 20 women referred to colposcopy at the Gynecology Clinic, San Gerardo Hospital. SCVS were collected first using FS, followed by PACS collection, using L-shape FLOQSwabs™ (Copan). The PACS were placed in 20mL PreservCyt (PC) (Hologic) while the SCVS were delivered dry to the Laboratory, of the University Milano-Bicocca. SCVS were suspended in 5mL PC Nucleic acid extraction was performed by NucliSENS®easyMAG (bioMérieux) and HPV was detected using AnyplexII™ HPV28 (Seegene). Sample cellularity was evaluated using an "in house" quantitative real-time PCR detecting human CCR5 gene. Later one ml aliquot of each SCVS was diluted 1:4 and retested for HPV.

Conclusion

Data obtained when performing HPV testing on dry-swabs eluted in 5 ml showed a very good concordance for high-risk HPV (hrHPV) detection between PACS and SCVS, with no evidence of inhibition. Excellent concordance in hrHPV detection was observed when comparing SCVS samples eluted in 5ml with those further diluted 1:4 (representing 20ml in PC). Adequate and comparable total sample cellularity for all PACS (mean value 2.67E+06 cells/sample) and SCVS (mean value 2.07E+06 cells/sample) samples was observed

References

Results showed a high degree of concordance in hrHPV detection between SCVS eluted in both 5ml and 20ml of PC as compared to PACS. This was further supported by the comparable and adequate total sample cellularity obtained from both PACS and SCVS using Copan FLOQSwab©. Standardization of an elution protocol for processing SCVS delivered dry to the laboratory would allow to reliably test samples for hrHPV detection and to compare results from different validation studies.

00339

NON-SPECULUM CLINICIAN SAMPLING FOR HPV TESTING TO INCREASE CERVICAL SCREENING UPTAKE IN WOMEN AGED 50 AND ABOVE

10. Self-sampling

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Background / Objectives

Women aged >65 account for a fifth of cervical cancers in the UK,(1) and around half of the deaths.(2) The majority are in women not adequately screened when aged 50-64,(3) but coverage continues to fall in this age group. Cervical screening with a speculum can become particularly uncomfortable after the menopause.(4) Self-sampling is a potential solution but 50%-70% of women worry about not taking a good sample.(5-8) HPV testing on clinician-collected vaginal samples without a speculum (non-speculum) is another possibility. Test performance would presumably be similar to self-sampling, but women would have the reassurance of a clinician-taken sample and could be particulalry attractive to postmenopausal women. Here we performed a cross-sectional study to examine test performance.

Results

Between Sep17-Jun18 non-speculum clinician samples and cytology (speculum samples) were collected from women aged 50-64 attending routine cervical screening in GP primary care and from women aged 50+ attending colposcopy (known or likely to be HPV positive). Samples were collected immediately before routine screening or colposcopy.

Sensitivity to high-grade disease (CIN2+) was assessed as the proportion HPV positive on non-speculum samples among histologically confirmed CIN2+ and among HPV positives on speculum samples. Specificity was assessed as the proportion HPV negative on non-speculum samples among women attending routine screening with <moderate dyskaryosis & <CIN2+.

Non-speculum samples were collected using a flocked swab (Copan 552C), transported dry, resuspended in ThinPrep prior to analysis using Roche Cobas4800.

Conclusion

Of 214 women attending routine screening, cytology samples could not be taken from 7 women because of pain/discomfort associated with the speculum. Of these, one had cytology subsequently collected, leaving 208 women with complete results: 198 were speculum HPV negative, all were <moderate dyskaryosis (none biopsied) and 96.5% (95%CI 92.9-98.6) were non-speculum HPV negative. Seven women were speculum negative/non-speculum positive – all cytology negative. The remaining 10 women were speculum positive/non-speculum positive (95%CI 69.2-100).

Of 46 women in colposcopy, 44 were speculum HPV positive, of these 90.5% (95%CI 72.6-94.8) were non-speculum positive. Of 7 with histologically confirmed CIN2+, all were non-speculum positive. Recruitment to this cohort will continue until Jan19.

References

Non-speculum clinician sampling for HPV testing is a viable option for older women. Preliminary data show that sensitivity is at least as good as speculum sampling for detecting HPV and CIN2+, but specificity may be lower. Findings should be confirmed in a larger study.

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00405

SELF-SAMPLING OF VAGINAL FLUID AND URINE FOR HIGH-RISK HUMAN PAPILLOMAVIRUS TESTING: AN OPTION FOR WOMEN PREVIOUSLY TREATED FOR HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA?

10. Self-sampling

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Background / Objectives

We assessed the performance of self-sampled vaginal fluid (VF) and first void urine (FVU) from women treated for CIN2+ for high risk HPV DNA (hrHPV) testing using a PCR-based clinically validated assay for cervical cancer screening by comparison to physician collected samples (REF).

Results

A prospective cohort of women with histopathology confirmed CIN2+ (N = 538); who underwent excisional treatment was followed-up at 6-months after treatment. Clinical assessment was carried out according to current standards of care including cytology, colposcopy and biopsy if the colposcopy indicated abnormal findings. VF (Qvintip, Aprovix) and FVU were collected by participants prior to sampling of a REF sample (PreservCyt, Hologic). Qvintip brush heads (air dried; stored at room temperature) were transferred into Cervi-Collect Tubes (Abbott) prior to testing. FVUs were mixed and transferred into Cervi-Collect Tubes within 30 minutes from collection and stored frozen until testing. Matched triplets of VF, FVU and REF samples were tested for the presence of hrHPV DNA (RealTime High Risk HPV, Abbott), following the manufacturer´s instructions.

Conclusion

A total of 484 matched triplets with valid PCR results were available for analysis. Good agreement of overall hrHPV (O) results was found between VF/FVU and REF samples (O-VF 88.6%, k 0.7; O-FVU 87.2%, k 0.6). High sensitivity for the detection of hrHPV in self-collected sample types versus REF was found with VF (90.5%; 95% CI:84.4–96.4), while the sensitivity for urine was (62.1%; 95% CI:52.4–71.9). In

contrast, the specificity of hrHPV detection in FVU was significantly higher versus REF (93.3%; 95% CI:90.8–95.8) than that in VF (88.2%; 95% CI:85.0–91.4). Sensitivity of hrHPV for the detection of residual/recurrent disease (HSIL/CIN2+) was 100% with REF samples and the specificity was 82.2% (95% CI:78.8-85.8). Somewhat lower sensitivity for the detection of residual/recurrent disease was found with VF (81.8%; 95% CI: 59.0 -100) and FVU (74.0%; 95% CI:46.4-99.1), respectively. Specificity of hrHPV for the detection of residual/recurrent disease (LSIL/CIN1) on FVU (83.7%; 95% CI:80.4-87.1) and was comparable to that of REF samples (83.7%; 95% CI:78.8 -85.8) and significantly lower on VF (74.0%; 95% CI:70.0 -78.0)

References

Good concordance of hrHPV detection between paired self-sampled VF/FVU and REF samples was observed in the ToC-setting. HrHPV testing of VF & FVU identified the majority of cases with residual/recurrent disease after 6 months detected by REF samples suggesting that hrHPV testing of both alternative sample types can be useful in follow up of women after treatment for high grade dysplasia. However, larger studies are required to confirm these findings

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00531

ACCEPTABILITY OF CERVICOVAGINAL SELF-SAMPLING IN CERVICAL CANCER SCREENING

10. Self-sampling

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Background / Objectives

Cancer of the uterine cervix is still a large public health problem mainly in poor regions,need for multiple consultation for follow-up,difficulty in quality control in the screening procedure and lack of resources to provide the necessary treatment. Some countries have explored alternative methods for the universalization and facilitation of access to cervical cancer screening, where self-sampling stands out. OBJECTIVE: To assess the results of vaginal self-sampling in cervical cancer screening and compare its acceptability against the collection performed by a health care professional.

Results

It is a prospective and cross-sectional study involving women over 21 years old. Participants (n = 214) were treated at the Gynecology outpatient clinic of the Hospital Universitário da Universidade de São Paulo (HU-USP) and Hospital das Clínicas das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP).

Conclusion

The participants had a mean age of 37.77 ± 11.06 years old, the majority of whom were white (62.3%) or brown (26.6%); 90.6% were in the menacme. Most women had only elementary school (literate, 45.7% and complete elementary school, 43.8%). In the obstetric history, 35.8% had 3 or more deliveries and 26.5% had only one delivery. The age of initial sexual activity was 16.78 ± 2.83 years (61.1% of cases from 15 to 18 years of age). Most women (35.6%) used a combined hormonal contraceptive method; condoms exclusively were used by 16.1% of the women. 71.8% were non-smokers and 71.9% reported not drinking alcohol; 98.5% reported not using any illicit drug. The following results refer to the questionnaire on the acceptability of cervicovaginal self-sampling. Regarding the understanding of the use

of the self-sampling brush (SSB), 50.48% considered it very easy; 45.71% considered it easy; 0.95% considered it a bit difficult; and none considered difficult. Regarding the effective use of the SSB, 38.10% considered it very easy; 55.24% considered easy; 3.81% considered it a bit difficult; and none considered difficult. During the use of the SSB, none reported much pain or discomfort; 4.76% reported pain or discomfort; 20.00% reported little pain or discomfort; and 72.38% reported no pain or discomfort. Besides that, none felt very embarrassed, 1.90% felt embarrassed, 19.05% felt little embarrassed and 76.19% did not feel embarrassed. Concerning the fear of getting hurt during the use of the SSB, 9.52% were afraid; 8.57% had little fear and 79.05% had no fear.

References

Most participants refer a good acceptability of cervicovaginal self-sampling with little or no discomfort, embarrassment, pain or fear during the procedure. Thus, due to its potential to increase the number of women screened, this procedure should be considered, above all, in public health policies.

FC 16. Self-sampling 2

00082

HPV SELF-TESTING/SELF-SAMPLING WILL SAVE INDIGENOUS LIVES

10. Self-sampling

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Background / Objectives

Māori (Indigenous) women experience unacceptably high rates of cervical cancer morbidity and mortality. Many Māori women find current cervical screening intrusive, resulting in low screening rates. ‘He Tapu Te Whare Tangata’ explored the acceptability of human papillomavirus (HPV) self-testing (/self-sampling) for never/under-screened Māori women to inform the New Zealand National Cervical Screening Programme.

Results

The study objectives were to explore under-screened Māori women’s reactions to HPV self-testing in hui (focus groups/interviews); survey Māori women about their HPV self-testing attitudes and potential behaviours; and canvasss key informants about HPV self-testing. A multi-disciplinary team, including elders and community based researchers (CBRs), conducted the Kaupapa Māori (by Māori, for Māori) research. CBRs ran hui with 106 eligible Māori women (aged >25 years, no screen in >4 years) in four regions, and arranged peer surveying (397 eligible surveys returned). The views of 16 key informants (KIs), including GPs and nurses, were canvassed.

Conclusion

A majority of survey participants were enrolled with a primary health care organisation (87%) and attended regularly (72%). However, they did not screen, with

‘whakamā’ (embarrassment/shyness/reticence) the most frequently given reason. Three in four participants said they were likely/very likely to do an HPV self-test, and 88% of women said they were likely/very likely to seek follow-up if required. Women and KIs agreed the delivery of test results should be tailored and that follow-up should be supported. Health practitioner cultural competence and empathy were emphasized.

References

When Māori women are engaged in the health system but do not screen, this is a system failure. The findings of this study indicate that with a culturally responsive, flexible HPV self-testing cervical cancer prevention programme (for example, available from community outreach workers at home visits and/or community centres, as well as opportunistically at clinics) many currently never/under-screened Māori women would be screened and followed-up if necessary. Recommendations to ensure optimum engagement with these women include: a strengths-based whole whānau approach to HPV education; and Primary Health Organisations working closely with community health providers to ensure standard recall, opportunistic in-clinic invitations to self-test, and targeted outreach. With well introduced HPV self-testing, many currently never/under-screened Māori women would be screened and followed up if necessary. HPV self-testing will save lives!

00249

EVALUATION OF SELF-SAMPLING FOR HPV AND STI TESTING AS AN ALTERNATIVE TOOL FOR WOMEN'S PARTICIPATION TO PREVENTION PROGRAMS

10. Self-sampling

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Background / Objectives

Self-sampling has been proposed as alternative tool to increase the participation of hard-to-reach women to prevention programs. The objective of this study was to evaluate the use of two different self-samples, vaginal and first-void urine samples, as compared to clinician-collected samples for the molecular detection of Human Papillomavirus (HPV) and other sexually transmitted infections (STIs) such as Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), Mycoplasma genitalium (MG), and Trichomonas vaginalis (TV).

Results

Physician administered cervical samples, self-collected vaginal samples using endo_eso_cervical and self-vaginal FLOQSwabs™ (Copan), and first-void urines using Colli-Pee (Novosanis) were collected from 82 women attending the Gynaecology Outpatients Clinic of San Gerardo Hospital (Monza, Italy) with a recent diagnosis of cervical dysplasia. Nucleic acids were extracted by NucliSENS easyMAG (bioMérieux) and HPV and STIs detection was carried out using AnyplexII™ HPV28 and AllplexTMCT/NG/MG/TV Assay (Seegene), respectively. Sample cellularity was evaluated by means quantitative real-time PCR detecting human CCR5 gene.

Conclusion

Preliminary data showed an adequate and comparable sample cellularity for all samples (mean value for urine, vaginal and cervical samples: 2.09E+06, 2.07E+06 and 2.67E+06 cells/sample, respectively). An optimal concordance for at least one high-risk HPV type detection compared to cervical sample (gold standard) was

demonstrated for both self-samples (k=0.95). HPV16 resulted the most frequently hrHPV type detected. HPV co-infections were shown in 51%, 55% and 64% of cervical, vaginal and urine samples, respectively. A higher STIs positivity was found in self-sampling samples compared to physician-collected samples with Chlamydia trachomatis being detected in 4% and 5% of clinician administered and self-sampling, respectively.

References

Cellularity of both self-collected and clinician-collected cervical samples using Copan endo_eso_cervical and self-vaginal showed comparable results and both HPV and STIs detection using molecular methods demonstrated a high degree of concordance. These data reveal promising results for the introduction of self-collected samples in cervical cancer and sexually transmitted infections screening programs.

00297

COMPARISON OF DIFFERENT SELF-SAMPLING DEVICES FOR SEXUALLY TRANSMITTED INFECTIONS (STI) AND HUMAN PAPILLOMAVIRUS (HPV) DETECTION USING MOLECULAR METHODS

10. Self-sampling

I. Sechi [1], M. Martinelli [2], R. Musumeci [2], G. Brenna [2], E. Calaresu [2], F. Perdoni [2], A. Piana [1], A. Cossu [1], N. Muresu [1], C. Cocuzza [2]

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Background / Objectives

Vaginal Self-collection for STI and HPV screening is generally well accepted by women, although this may raise patients' concerns on their ability to collect adequate samples, particularly as some devices may require more extensive manipulations. Copan developed the vaginal self-collection FLOQSwab©(FS) suitable for STI and HPV screening with molecular assays.

The objective of this study was to compare FS to two other self-collection devices: Evalyn®Brush (EB) (Rovers Medical) and HerSwab(HS) (Eve Medical) for:

1. Performance of devices for HPV and STI molecular detection as compared to professional cervical collection;
2. Ease of use of devices for sample collection;
3. Costs of collection devices.

Results

Self-collected vaginal samples (SCVS) and physician administered cervical samples (PACS) were collected from women referred to colposcopy at the Gynecology Clinic, San Gerardo Hospital. SCVS were collected from 20 patients each using FS, HS and EB alternating the order of collection for each device, lastly PACS were collected. Self-collection procedures, provided by each manufacturer, were used and a questionnaire to evaluate the ease of use, self-sampling level of satisfaction and acceptability was completed by participants.

The PACS were placed in 20mL PreservCyt (Hologic) while the SCVS were delivered dry to the Microbiology Laboratory, University Milano-Bicocca. All SCVS were suspended in 5mL PreservCyt. Nucleic acid extraction was performed by means NucliSENS®easyMAG (bioMérieux) and STI and HPV was detected using AnyplexII™ HPV28 and Allplex™ CT/NG/MG/TV Assay (Seegene). Costs analysis for purchasing each self-collection devices was performed.

Conclusion

Data obtained showed an excellent STI and high-risk HPV (hrHPV) detection concordance between PACS and SCVS using both FS and HS (k=0.95). A good concordance (k=0.75) was demonstrated comparing cervical samples and both FS and EB samples for both STI and HPV. Most women did not experience any problems when using the 3 different self-collection devices. Ninety-two percent of women declared to prefer self-sampling to undergoing gynaecological visit for testing. Cost analysis revealed that whilst FS is available at 0,60 - 0,70 Euro, EB and HS are approximately 4 and 9 times more expensive.

References

Preliminary results showed a high degree of concordance in STI and HPV detection between SCVS and PACS. Self-sampling, was preferred by women over PACS. In particular FLOQSwabs®, proved to be easier to use and cheaper as compared to other devices. Self-collection appears to be promising alternative to improve women's participation to STI and HPV screening programmes.

00369

VAGINAL SELF-COLLECTION VERSUS CERVICAL CLINICIAN-COLLECTED SAMPLES FOR CERVICAL CANCER SCREENING: WHAT WOULD YOU CHOOSE? RESULTS FROM SELF SAMPLING SATISFACTION QUESTIONNAIRES

10. Self-sampling

G. Fantacci [1], C. Sani [1], E. Burroni [1], A. Mongia [1], S. Bisanzi [1], G. Pompeo [1], F. Cellai [1], A. Iossa [2], G. Grazzini [2], C. Di Pierro [2], E. Cavazza [2], C.B. Visioli [3], C. Nicolai [4], L. Solfanelli [4], A. Lombardi [5], F. Carozzi [1]

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Background / Objectives

An ongoing ISPRO (Florence) research project on self-collection involved 5200 “non-responder” women: some performed sample collection at the clinic; others received at home “Dry” self-sampler device FLOQSwab®(Copan) or “Wet” device, containing 1 ml of MSwab®(Copan) both together with a satisfaction questionnaire, designed with the purpose to investigate the acceptability of self-collection rather than of clinician-collection of the sample.

Results

The questionnaire consists of three areas: easy of use of the self-collection system, possible physical problems (pain or bleeding) related to the use of the self-collection device and expression of preference between self-collected and physician-taken cervical sample. The results were evaluated with an average score, based on the scores given to each question. “Chi-square test” was used to compare the difference between scores.

Conclusion

The questionnaire was compiled by 99% of women who attended self-sampling: 90.6% found the self-collection system very easy/easy and 97.8% found easy the collection procedure and understood the instructions for the withdrawal. Related to the self-collection, discomfort or bleeding, 92.2% had no pain; finally, 81.4% of women preferred self-collection method rather than cervical clinician collection. There was no significant differences ($p>0.05$) between the two arms for type of self-sampling device methods or by level of education.

References

From questionnaire, it emerges that most of women found self-collection procedure easy or very easy; they did not report any particular pain, discomfort or bleeding and preferred self-collection, “Dry” or “Wet”, for reasons of time and comfort. Therefore, there is a good acceptability of the self-sampling system.

00381

URINARY HPV DNA TESTING AS A TOOL FOR CERVICAL CANCER SCREENING IN FRANCE: AN UPDATE OF THE CAPU-3 STUDY

10. Self-sampling

C. Lefeuvre [1], A. Pivert [1], T. Bickert [1], M. Boitel [1], R. Houlet [1], A. Marchand [1], G. Michel [1], P. Veillon [1], F. Lunel Fabiani [1], A.S. Le Duc Banaszuk [2], A. Ducancelle [1]

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Background / Objectives

In France, cervical cancer screening is currently based on cytological examination of a Pap smear for women aged 25 to 65, but screening coverage is unsatisfactory. Previous studies in our lab have shown that urinary HPV testing for high-risk human papillomavirus (HR HPV) testing increases rates of compliance (1,2). Since November 2016, the CapU-3 study aims to invite 13,000 women aged 35 to 65 who did not performed a Pap smear over the past 7 years in Maine et Loire department. 500-700 letters proposing an at-home urinary HPV testing are sent monthly. With the letter, the women receive an urinary HPV DNA testing information note, a letter of informed consent, a sterile container, a procedure protocol, a bubble envelope and a prepaid return envelope. Women accepting to participate send their first-stream urine samples by mail to the Angers University Hospital Virology Laboratory using the bubble envelope and the prepaid envelope in accordance with a three-rule secure packaging protocol as recommended in France. The end of the study is scheduled for November 2018.

In collaboration with Cap Santé 49, we conducted a pilot study to offer urinary HPV testing for women who don't have regular cervical smear in order to increase the cervical cancer screening coverage in our department.

Results

HR HPV detection is performed using a real-time PCR technique (Anyplex II HPV28 Detection) that detects 28 genotypes. Patients with HPV-positive results are encouraged to perform a cervical smear as soon as possible to detect the presence

of cervical lesions. For HPV-negative women, a Pap smear within 1 year is recommended for those women who do not have regular gynecological follow-up.

Conclusion

After exclusion (past hysterectomy or refusal), the participation rate is 14.2% (CI95%: 13.6%-14.8%).

Out of the 1637 analyzed specimens, 1450 and 168 were negative and positive for at least 1 HR HPV respectively. HR HPV others than HPV 16 or HPV 18 were mostly detected as HPV 53 (15.8%; CI95%: 11.3%-21.7%) and HPV31 (10.5%; CI95%: 6.9%-15.7%).

Invalid results occurred in only 19 samples.

Among the cervical smears performed in positive patients, 4 high-grade cytological lesions have already been detected.

References

Because home HPV urinary testing is non-invasive and do not require medical attention, this method may be an alternative for women who are reluctant to use Pap smear. Furthermore, 70.5% of the HPV-positive women included in the CapU3 study benefited from a Pap smear collected by a clinician during follow-up. So, the urinary HPV test could be an alternative to the usual screening by cervical smear thus extending screening coverage in our department.

References

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00452

Temperature and time stability of self-collecting samples in Japan where the temperature sometime reaches over 35-40 degrees Celsius in summer

10. Self-sampling

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Background / Objectives

In the past few years, we have conducted some trial studies to improve the coverage of the population based cervical cancer screening using self-collecting HPV test in Japan because Japanese coverage of the screening is so low that incidence and mortality of cervical cancer is increasing especially in younger generations such as late 20s and early 30s. Acceptance of the participants was widely accepted and they preferred the self-collecting HPV test much more than the conventional cytology test the Japanese government recommends. We use Evalyn Brush as a self-collection device which the Netherlands and Denmark use for non-responding people for their national cervical cancer screening programs. However, in Japan, the summer temperature often soars to over 35 degrees Celsius and has reached 40 degrees in some parts this year. The temperature of public mailboxes in some towns has reached around 50 degrees Celsius. The samples of self-collecting HPV tests are sent to the testing laboratory through the postal service and could be exposed to sweltering environments.

We want to make sure if the self-collecting HPV test sample using Evalyn Brush is stable in a high temperature environment such as a summer in Japan. If we can find out how high environment temperature the sample can sustain, it must be useful information in other parts of Asia.

Results

We get 2 samples from the same participant via physicians using Evalyn Brush. After collecting and sending the samples to the testing laboratory, one sample is tested as a normal test and another one is kept in 4 conditions and tested as an experimentally

high temperature environmental test; First in 50 degrees Celsius for 2 weeks; Second in the same temperature for 4 weeks; Third in 30 degrees Celsius for 2 weeks; fourth, in the same temperature for 4 weeks. We are planning a collection sample size of approximately 20 samples per group for a total of 80 samples. We compare the results of the samples from the same participant and confirm if there is a difference.

Conclusion

Our study is ongoing as of August 2018.

References

We will be able to report the entire result at the EUROGIN 2018 conference.

00459

An effective 3-gene methylation classifier for direct triage on hrHPV-positive self-samples

10. Self-sampling

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Background / Objectives

Offering self-sampling of (cervico-) vaginal material for high-risk HPV (hrHPV) testing is an effective method to increase the coverage in cervical screening programs. However, an additional triage test directly applicable to self-sampled material is necessary to identify hrHPV-positive women at risk for progression to cervical cancer. Since cytology cannot be reliably performed on self-sampled material, there is a need for molecular triage markers. Candidate molecular disease markers for triage testing involve the host cell epigenetic changes, such as DNA hypermethylation, that following a transforming hrHPV infection drive progression to cancer. Earlier work has shown that methylation analysis virtually detects (virtually) all cervical carcinomas and advanced CIN2/3 lesions. Longitudinal outcome data in an hrHPV-positive screening cohort illustrate a low 14-year cervical cancer risk among baseline methylation-negative women as compared to baseline cytology–negative women. Here, we set out to identify and validate a DNA methylation classifier for detection of cervical precancer (CIN3) and cancer, applicable to self-samples.

Results

We determined genome-wide DNA methylation profiles of 72 hrHPV positive self-samples, from screening non-attendees using the Infinium Methylation 450K Array, and further evaluated the selected DNA methylation markers by multiplex quantitative methylation-specific PCR (qMSP). Logistic regression analysis was performed to build a DNA methylation classifier for CIN3 detection applicable to self-samples. For validation, an independent series of HPV-positive self-samples was used.

Conclusion

Genome-wide DNA methylation profiling revealed 12 DNA methylation markers for CIN3 detection. Multiplex qMSP analysis of these markers in large series of self-samples yielded a 3-gene methylation classifier (ASCL1, ST6GALNAC5 and LHX8). This classifier showed a good clinical performance for CIN3 detection in HPV-positive self-samples in the validation set. Importantly, all self-samples from women with cervical cancer scored DNA methylation-positive.

References

A highly effective 3-gene methylation classifier for direct triage on hrHPV-positive self-samples was identified using a genome-wide DNA methylation profiling. Our findings indicate that a transition towards full molecular self-screening in hrHPV-based cervical screening programs is feasible. The study findings are currently evaluated in a self-sampling study cohort from the regular screening population.

00316

UTILITY OF URINE ONCOGENIC HPV TESTING FOR DIAGNOSIS OF CIN 2+

13. Screening methods

L. Rahangdale [1], A. Knittel [1], C. Edelman [2], B. Sanusi [3], S. Tulenko [4], L. Romicki [5], V. Sivaramam [5], S. O'connor [6], J. Nelson [7], J. Schmitt [8], B. Faherty [9], K. Chesko [9], L. Vaughan [9], J.S. Smith [10]

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Background / Objectives

Cervical cancer incidence and death are highest among medically underserved women in the U.S. Urine testing for hrHPV (high risk) as a primary screening test may be more acceptable and accessible to at-risk women. We aimed to assess the validity of testing for oncogenic HPV in urine for the detection of high-grade cervical precancer (CIN2+).

Results

Self-collected urine, self-collected cervico-vaginal and physician-collected cervical samples were obtained from women undergoing clinically-indicated cervical colposcopy or excisional procedures at the University of North Carolina and Duke University medical centers. Women with normal cytology and positive hrHPV test results were also recruited and underwent colposcopy. Samples were tested for high risk (HR) HPV E6/E7 DNA using the BD Onclarity HPV Assay (Becton Dickinson, New Jersey, USA). Sensitivity, specificity, positive and negative predictive values were calculated for detection of CIN 2+ histology for urine and for cervico-vaginal

self-collected specimens. Agreement between the sample collection methods was assessed by Cohen’s kappa statistic (κ) and percentage agreement.

Conclusion

Between Nov 2016 and Aug 2018, a total of 315 women ages 25–65 years (median age=36) had valid HPV testing results on all 3 sample collections and on cervical histology. Most women were either uninsured (41%) or had Medicaid/Medicare (21%). A third (36%) were privately insured, with half (48%) self-identifying as White, and 29% as Black. The Assay performance in each of the sample types is summarized in Table 1. The overall concordance among the three tests was 70.0% (κ =0.5, p < .0001). There was 74.6% agreement the urine and physician tests (κ = 0.44, p < .0001), 83.6% agreement between self-collected urine and cervico-vaginal tests (κ = 0.7, p < .0001), and 74.5% agreement between cervico-vaginal and physician tests (κ = 0.45, p < .0001).

TABLE 1	Sensitivity	Specificity	PPV	NPV
Provider-collected	89.2%	50.7%	46.4%	90.8%
Cervico-Vaginal self-collected	89.2%	29.6%	37.8%	85.1%
Urine self-collected	93.1%	27.7%	38.2%	89.4%

References

Self-collected urine hrHPV testing had similar performance to self-collected cervico-vaginal HPV testing. The option of self-testing for hrHPV may improve cervical cancer screening for women with limited access to healthcare.

00482

COMPARISON OF A DNA METHYLATION CLASSIFIER WITH HPV16/18 GENOTYPING AND REPEAT CYTOLOGY TRIAGE FOR DETECTION OF CIN2+ IN HPV POSITIVE WOMEN WITH ASC-US INDEX CYTOLOGY

16. Methylation

A.T. Lorincz [1], G.I. Sanchez [2], B. Nedjai [1], M.C. Agudelo [2], J.D. Villa [3], M.C. Kelly [3], A.R. Brentnall [1], J. Cuzick [1], T.A. Ramirez [2]

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Background / Objectives

HPV16/18 genotyping and cytology are proposed as triage tests for proper referral to colposcopy of HPV positive women. We compared HPV16/18 genotyping and repeat cytology with the new DNA methylation test S5 (based on weighted methylation measurements of gene regions, including human gene EPB4IL3, and late gene regions of HPV16, HPV18, HPV31 and HPV33) in HPV positive women with ASC-US index cytology.

Results

167 women with expert confirmed CIN2+ and 167 age- and date of diagnosis matched controls (<CIN2) were identified in a cohort with ASC-US index cytology, followed-up in routine clinical services for 24 months. Archived HPV positive samples from the recruitment visit were HPV genotyped and tested for methylation, blinded to cytology, histology and initial HPV results. The sensitivity and specificity of cytology was determined using the worst cytology repeated at 6 or 12 months after the ASC-US index cytology, at a threshold of ASC-US or above. The performance of HPV genotyping and S5 were determined from baseline specimens. At our standard cut-off of 0.8 (previously validated for a screening population) for the continuous S5 classifier, and also in a post-hoc analysis with the S5 cut-off at the upper quintile

(3.1) of the control group, the S5 values were used to dichotomize methylation results as positives and negatives.

Conclusion

S5 median methylation level was 1.06 in histology Negative (n=125), 1.42 in CIN1 (n=42), 3.72 in CIN2 (n=123), 8.0 in CIN3 (n=40) and 10.84 in cancer (n=4) (Cuzick test for trend $\chi 2 = 42.6$, $p < 0.001$). Sensitivity of HPV16/18 genotyping was 52% (95%CI: 43-61%) and of cytology was 28% (95%CI: 17-39%). Performance of S5 at the pre-defined screening cut-off of 0.8 had poor specificity (sensitivity 84%, 95%CI: 79-89%; specificity 34%, 95%CI: 27-44%) which was significantly ($p < 0.001$) lower than the specificity of HPV16/18 (64%, 95%CI: 56-71%) or cytology (79%, 95%CI: 73-84%). In contrast at a cut-off 3.1 sensitivity of S5 was 58% (95%CI: 50-66%), similar to the sensitivity (52%) of HPV16/18 testing and much better than the sensitivity of cytology. Also, the specificity of S5 at this cut-off was 74% (95%CI: 67-80%), significantly higher than for HPV16/18 testing ($p=0.03$) and similar to cytology ($p = 0.38$). The AUC of the continuous S5 classifier (0.71, 95%CI: 0.65-0.77) was significantly higher (Delong test <0.001) than the AUC of either HPV16/18 (AUC: 0.58, 95%CI: 0.52-0.64), cytology (AUC: 0.54, 95%CI: 0.48-0.60) separately, or both combined (0.57, 95%CI: 0.51-0.63).

References

S5 was superior to cytology, HPV16/18 genotyping or their combination, for detecting CIN2+ in HPV+ women with an ASC-US index cytology.

FC 17. Methylation 2

00128

METHYLATION IN HPV16 E2 BINDING SITES 3/4 IS INDEPENDENT OF GLOBAL HOST GENOME METHYLATION AND RELATED TO SURVIVAL IN A COHORT OF OPSCC PATIENTS

16. Methylation

M.S. Kalteis [1], M. Reuschenbach [1], S. Vinokurova [2], U. Keilholz [3], A. Zakarneh [4], I. Tinhofer [5], M. Von Knebel Doeberitz [1], E.S. Prigge [1]

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Background / Objectives

The HPV16 upstream regulatory region (URR) undergoes shifts in methylation during HPV-induced carcinogenesis. Four binding sites for E2 (E2BS), a key regulatory protein of HPV E6/E7 oncogene expression, are located there. Methylation of these sites prevents E2 from fulfilling its function and thereby in turn promotes the overexpression of the E6 and E7 oncogenes which is the key step in HPV-induced tumorigenesis.

We have shown previously that shifts in E2BS methylation occur during metastasis formation in oropharyngeal squamous cell carcinomas (OPSCC). We hypothesized that these changes in the HPV genome's epigenetic signature occur in a specific manner independent of global host genome methylation status and could be indicative of a distinct functional role of E2BS methylation in HPV-driven OPSCC. Additionally, changes in E2BS methylation might be related to clinical outcome.

Results

Formalin-fixed, paraffin-embedded tissue sectioned from 67 simultaneously HR-HPV 16-driven, i.e. HPV16 DNA+ and $p16^{INK4a}$+, tumors (42 OPSCC primaries with 25 matched lymph-node metastases) was obtained from a German OPSCC cohort along with corresponding clinical data. Bisulfite-converted DNA was analyzed for methylation ratios in 4 CpGs in E2BS3 and 4 as well as 3 CpGs in the LINE1 retrotransposon by pyrosequencing. Cut-offs for low/high methylation were

established using cluster analysis. Kaplan-Meier-curves and log-rank-tests were utilized to examine overall and progression-free survival (OS, PFS).

Conclusion

Lower methylation levels could be observed in all E2BS CpGs in lymph node metastases when compared to their matched OPSCC primaries, with this difference reaching statistical significance for the CpG at position 43 in E2BS3 (p=.02). There was no significant difference detectable in LINE1 methylation as a marker of global genome methylation between primary tumors and their corresponding metastases. High E2BS methylation in primary tumors (> 52%) was associated with both reduced OS and PFS.

References

Shifts in E2BS methylation in OPSCC occur in specific patterns that are not associated with global host genome methylation as assessed in LINE1 retrotransposons in our cohort of HPV-driven primary tumors and associated metastases. Furthermore, these changes in epigenetic markup were found to be associated with clinical outcome parameters. These findings suggest that distinct HPV16 URR methylation patterns play a functional role during OPSCC progression and have an impact on patient survival.

00164

DETECTION OF HYPERMETHYLATED GENES AS MARKERS FOR CERVICAL SCREENING IN WOMEN LIVING WITH HIV

16. Methylation

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Background / Objectives

To evaluate the performance of hypermethylation analysis of *ASCL1*, *LHX8* and *ST6GALNAC5* in physician-taken cervical scrapes for detection of cervical cancer and cervical intraepithelial neoplasia (CIN) grade 3 in women living with HIV (WLHIV) in South Africa.

Results

Samples from a prospective observational cohort study were used for these analyses. Two cohorts were included: a cohort of WLHIV who were invited for cervical screening (n=321) and a gynaecologic outpatient cohort of women referred for evaluation of abnormal cytology or biopsy proven cervical cancer (n=108, 60% HIV seropositive). Cervical scrapes collected from all subjects were analysed for hypermethylation of *ASCL1*, *LHX8* and *ST6GALNAC5* by multiplex quantitative methylation specific PCR (qMSP). Histology endpoints were available for all study subjects.

Conclusion

Hypermethylation levels of *ASCL1*, *LHX8* and *ST6GALNAC5* increased with severity of cervical disease. The performance for detection of CIN3 or worse (CIN3+) as assessed by the area under the receiver operating characteristic (ROC) curves (AUC) was good for *ASCL1* and *LHX8* (AUC 0.79 and 0.81, respectively), and

moderate for *ST6GALNAC5* (AUC 0.71). At a threshold corresponding to 75% specificity, CIN3+ sensitivity was 72.1% for *ASCL1* and 73.8% for *LHX8* and all samples from women with cervical cancer scored positive for these two markers.

References

Hypermethylation analysis of *ASCL1* or *LHX8* in cervical scrape material of WLHIV detects all cervical carcinomas with an acceptable sensitivity and good specificity for CIN3+, warranting further exploration of these methylation markers as a stand-alone test for cervical screening in low-resource settings.

00207

Host-cell DNA methylation patterns during high-risk HPV-induced carcinogenesis reveal a heterogeneous nature of cervical pre-cancer

16. Methylation

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Background / Objectives

Cervical cancer development following a persistent infection with high-risk human papillomavirus (hrHPV) is driven by additional host-cell changes, such as altered DNA methylation. In previous studies, we have identified 12 methylated host genes associated with cervical cancer and pre-cancer (CIN2/3). This study systematically analyzed the onset and DNA methylation pattern of these genes during hrHPV-induced carcinogenesis using an longitudinal in vitro model of hrHPV-transformed cell lines (n=14) and hrHPV-positive cervical scrapings (n=113) covering various stages of cervical carcinogenesis.

Results

DNA methylation analysis was performed by quantitative methylation-specific PCR (qMSP) and relative qMSP values were used to analyze the data.

Conclusion

The majority of genes displayed a comparable DNA methylation pattern in both cell lines and clinical specimens. DNA methylation onset occurred at early or late immortal passage, and DNA methylation levels gradually increased towards tumorigenic cells. Subsequently, we defined a so-called cancer-like methylation-high pattern based on the DNA methylation levels observed in cervical scrapings from

women with cervical cancer. This cancer-like methylation-high pattern was observed in 72% (38/53) of CIN3 and 55% (11/20) of CIN2, whereas it was virtually absent in hrHPV-positive controls (1/26).

References

In conclusion, hrHPV-induced carcinogenesis is characterized by early onset of DNA methylation, typically occurring at the pre-tumorigenic stage and with highest DNA methylation levels at the cancer stage. Host-cell DNA methylation patterns in cervical scrapings from women with CIN2 and CIN3 are heterogeneous, with a subset displaying a cancer-like methylation-high pattern, suggestive for a higher cancer risk.

00247

HR-HPV INFECTION AND THE METHYLATION OF P16INK4A IN WOMEN WITH HSIL IN CERVIX BEFORE AND AFTER TREATMENT.

16. Methylation

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Background / Objectives

One of the mechanisms by which high-risk human papillomavirus (hr-HPV) alters DNA methylation profile is targeting the epigenetic mechanisms through enzymes (Anayannis, Schlecht, and Belbin 2015). The methylation of p16 was found as a risk factor for ASCUS/LSIL progression to HSIL (Lee and Lee, n.d.). However, there is a lack of research on follow-up outcome for women with HSIL with methylated p16 after treatment.

Results

In the pilot, longitudinal cohort study 25 women with the diagnosis of HSIL were included in Antônio Pedro University Hospital, Brazil in 2011-2012. Methylation-specific polymerase chain reaction was performed using cytology samples collected before surgery and 6 months after to evaluate methylation of the p16INK4a. Hr-HPV was detected using HPV E6/E7 mRNA in situ hybridization.

Conclusion

Hr-HPV infection was found in 72.0% (18/24) cases. Promoter methylation of p16INK4a occurred in 72.0 (18/25) cases, but significantly did not differ between hr-HPV positive (72.2%, 13/18) and negative (66.7%, 4/6) samples (OR 1.3, CI95% 0.2-9.5, p =1.0). Expression of p16INK4a was found in 52.0% (13/22) and commonly detected together with methylated p16INK4a (66.7%, 10/15), however, the result has

not reached statistical significance (p=0.4). The silencing of p16INK4a was not significantly associated with methylation status, even in HPV-infected samples in which the p16INK4a promoter was methylated (>0.05).

In CIN III group all but one had the persistence of the same or higher expressed promoter methylation of p16INK4a after surgery (Wilcoxon Sing rank test p=0.02). This trend was evident in total sample as well (Wilcoxon Sing rank test p=0.01), but was not related to immunohistochemically detected expression of p16INK4a in tissue (Mann-Whitney U p=0.9), hr-HPV diagnosis before (Mann-Whitney U p=0.3) and after surgery (Mann-Whitney U p=1.0), compromised margins (Mann-Whitney U p=0.4), grade of lesson (Kruskal Wallis Test p = 0.3).

References

Methylation of p16INK4a is the evident process in women with cervical lesions. The process is noticed even after surgery, thus more research is necessary to clarify it's clinical and pathophysiological significance.

References

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00360

SIX METHYLATION MARKERS, KNOWN AS GYNTECT ASSAY, SHOW A VERY GOOD PERFORMANCE IN A TRIAGE SETTING ON HPV POSITIVE WOMEN

16. Methylation

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Background / Objectives

HPV DNA testing as a primary screening marker is being implemented in several countries. Due to the high HPV prevalence in the screening population, effective triage strategies for HPV-positive cases are required. The aim of this study was to evaluate the performance of a methylation-specific real-time PCR assay (GynTect) comprising six marker regions as a triage test.

Results

In a retrospective, cross-sectional study with the colposcopy clinic of Jena University Hospital, cervical scrapes from 675 patients were analyzed using methylation specific PCR for 6 (ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671) promising DNA methylation marker regions, called GynTect markers. We correlated the GynTect results to histopathological findings.

Conclusion

The GynTect methylation markers show a 100% sensitivity for CIS and cancer scrapes (n=31), irrespective of suptype. 64.1% CIN3 were detected followed by 30% CIN2 and 12.5% CIN1, respectively. In the HPV positive, but biopsy proven “no CIN group”, of 19.2% GynTect are positively tested. In total, sensitivity and specificity for CIN3+ in this cohort was 72.4% and 85.2%, respectively.

In contrast, real negatives from routine screening (HPV negative and Pap I, n=545) show an extra ordinary low positivity rate for GynTect® of 1.1%.

References

The performance of the GynTect assay based on cervical scrapes from the colposcopy clinic in Jena provides good evidence for the usefulness of methylation markers to detect HPV-positive women with clinically relevant disease.

00362

A PANEL OF SIX DNA METHYLATION MARKERS, COMPRISING THE GYNTECT CERVICAL CANCER TRIAGE TEST, DISPLAY EXCELLENT SENSITIVITY FOR CERVICAL CARCINOMAS

16. Methylation

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Background / Objectives

A prerequisite for triage tests complementing HPV-based cervical cancer screening, which now is or is being established in several countries (USA, the Netherlands, Ireland, Australia, Germany), is to detect cervical cancer with high sensitivity at no loss of specificity. DNA methylation has been discussed by experts as an attractive option in that context, and with GynTect a molecular diagnostic test is available based on this class of markers. The aim of this study was to assess the methylation of the six markers comprising GynTect in cervical carcinomas using both, cervical tissue and cervical scrapes.

Results

DNA isolated from 155 cervical cancer tissues as well as scrapes from 79 cancer and 14 CIS/ACIS patients taken before surgical treatment at the university women's hospital in Jena were included in the study comprising squamous cell carcinomas as well as adeno carcinomas. Methylation of the six marker regions ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671 was assessed performing methylation-specific PCR on chemically treated DNA from the cancer samples.

Conclusion

All 155 cervical tissues showed methylation of at least two of the six markers, and each of the methylation markers was positive in at least 80% of the cervical cancer tissues. Similar results were obtained when analysing the methylation of the six markers using the GynTect assay for the cervical scrapes from cancer and CIS/ACIS patients.

References

The six DNA methylation markers can be detected in tissue as well as scrapes obtained from cervical cancer patients with different sensitivities, ranging from 95% to 100%. The CE IVD marked GynTect assay for cervical cancer triage that is based on detection of these six markers, allows detection of all CIS/ACIS and all cancer cases with 100% sensitivity. Detection rates are irrespective of the type of cancer, allowing the reliable detection of both, squamous cell carcinomas and adeno carcinomas.

00389

Is human papillomavirus DNA methylation an accurate diagnostic marker for detection of women with abnormalities at cervical cancer screening?: A Systematic Review and Meta-analysis.

16. Methylation

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Background / Objectives

The introduction of HPV DNA testing for primary cervical screening aims to improve sensitivity of the screening. It will also increase positive test results and the best policy for triage of HPV-positive women is still unclear. Viral DNA methylation has been proposed as a novel biomarker for triage with encouraging but conflicting results. We undertook a systematic review and meta-analysis of published literature to assess the correlation of HPV DNA methylation with disease grade for prediction of high-grade intraepithelial disease (CIN2+).

Results

We searched electronic databases MEDLINE, EMBASE and CENTRAL. Studies were eligible if HPV epigenome was analysed by any DNA methylation method, with corresponding cytology or histology results available. Data were pooled and meta-analysed using random effects models in STATA.

Conclusion

42 studies were eligible for inclusion. Increasing methylation of the HPV16 L1 gene showed the greatest association with increasing disease grade (Normal: 14% (95%CI 3-37); CIN1: 42% (95%CI 7-83); CIN2: 53% (95%CI 5.2-98); CIN3: 77% (95%CI 29-100); invasive cervical cancer (ICC): 77% (95%CI 55-95). Pooled methylation percentage was significantly higher in CIN2+ vs. CIN2- (72.8% (95%CI 49-92) vs.

44% (95%CI 16-74), p<0.0001). For bisulphite sequencing methods only, overall pooled estimated odds ratio (OR) (95%CI) for high methylation in the HPV16 L1 gene for CIN2+ vs. CIN2- was 2.15 (95%CI 0.82-5.6), I290.6%. For pyrosequencing methods, the highest OR was observed at CpG site L1 5602 (OR 36.8, 95%CI 8.8-153). Pooled sensitivity and specificity for diagnostic accuracy of HPV16 L1 methylation in detection of CIN2+ were 0.83 (95%CI 0.74-0.90) and 0.62 (95%CI 0.54-0.69) (AUC 0.75 (0.71-0.79), I290% (95%CI 81-100)).

References

HPV16 L1 gene methylation levels correlate with increasing grade of CIN, with significantly higher methylations levels observed in CIN2+ vs. CIN2-. Sensitivity and specificity are highly variable by CpG site and estimates vary significantly between studies. Our results suggest that HPV methylation could be an accurate marker of high grade disease, but the genes and CpG sites most discriminatory must still be identified for clinical practice, and the role of methylation as a diagnostic test to triage HPV-positive women warrants further investigation.

00391

HOST DNA METHYLATION PANEL VS CYTOLOGY FOR HR-HPV POSITIVE CASES TRIAGE

16. Methylation

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Background / Objectives

There is strong agreement in the scientific community regarding the superiority of high risk (hr) HPV testing compared to cytology in cervical cancer primary screening. Limited specificity of hr-HPV testing, however, requires new biomarkers for the triage of HPV-positive cases, in order to avoid overtreatment and excessive referral to colposcopy. In fact, this lack of specificity of hr-HPV testing leads to a risk of overloading colposcopy. DNA methylation (viral and host) has been proposed as a promising strategy for triaging HPV-positive women in order to overcome this problem. This work aims to evaluate the potential of a host DNA methylation panel (Hansel et al., 2014; Schmitz et al., 2017) as an alternative to reflex cytology in triage.

Results

A maximum of 100 consecutive PreservCyt samples positive for hr-HPV testing (Roche COBAS® HPV) were selected from routine screening at LAP Unilabs Porto. For all these samples, cytology was performed (ASCUS and above considered cytology positive). Follow-up histology data generated for each patient will be included if available. Information regarding the evaluation sample, patient information and data regarding other clinical samples results relating to that patient were taken from the laboratory database to allow the clinical significance of the results to be assessed. All data stored for the evaluation were anonymized.

All DNA methylation panel testing was performed in the COBAS Z480 analyzer (component of the COBAS4800® system, which was used for HPV screening).

According to previous data generated for this host DNA methylation panel, we will assume a 100% sensitivity for cervical invasive carcinomas. To assume this performance in this study we will include at least ten cervical carcinomas in parallel to confirm it.

References

Data has been collected and is not fully available at the present time. We expect a lower positivity rate in the methylation panel, leading to increased specificity – without losing sensitivity - compared to cytology and therefore, with this approach reduce substantially the required number of colposcopy procedures. Comparing the costs of both approaches a cost effectiveness analysis could be performed and evaluate the viability of methylation analysis.

References

Hansel, A., Steinbach, D., Greinke, C., Schmitz, M., Eiselt, J., Scheungraber, C., … Dürst, M. (2014). A promising DNA methylation signature for the triage of high-risk human papillomavirus DNA-positive women. PLoS ONE, 9(3). http://doi.org/10.1371/journal.pone.0091905

00441

COMPARISON OF TWO METHYLATION BASED DIAGNOSTIC ASSAYS ON A COHORT OF CA 130 HPV POSITIVE CERVICAL SCRAPES: GYNTECT AND QIASURE

16. Methylation

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Background / Objectives

HPV DNA testing as a primary screening marker is being implemented in several countries. Due to the high HPV prevalence in the screening population, effective triage strategies for HPV-positive cases are required. Methylation markers are presently discussed as a suitable tool for triaging HPV positive women. We compared the two assays GynTect and QIAsure.

Results

In a retrospective setting 130 samples from the colposcopy clinic of the university hospital in Jena, all tested HPV positive, were tested with GynTect, comprising 6 (ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671) different methylation and QIAsure, comprising 2 (FAM19A4, mir124) methylation markers. The cohort comprises 7 cervical cancer scrapes, 49 CIN3, 8 CIN2 and 5 CIN1 and 59 no CIN samples. In addition, 10 HPV negative Pap I samples were tested.

References

Analyses are still ongoing and should be completed for the meeting. We expect a similar detection rate regarding the cancer cases and CIN2 and CIN3 samples. Looking at the no CIN group, higher detection rates are published for QIAsure assay (IFU) as compared to the GynTect assay. A direct comparison between both methylation marker panels has never been done so far.

00443

PERFORMANCE OF GYNTECT®, A DNA METHYLATION MARKER PANEL-BASED DIAGNOSTIC TEST, ON A WIDELY USED PCR DIAGNOSTICS PLATFORM

16. Methylation

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Background / Objectives

A change of the current screening algorithms to an HPV-based screening setting is discussed in several countries due to higher sensitivity of HPV testing compared to cytology. Reliable triage methods, ideally performed from the sample obtained for screening are, however, essential in such a setting to avoid overtreatment and higher screening costs. Specific DNA methylation patterns may provide a suitable triage tool, and they can be detected using molecular tests that do not require specific equipment.

Results

Cervical scrapes collected in PreservCyt® solution from women with cervical cancer (35 cases), CIN 1-3 (120 cases) and normal cytology (Pap I; 200 cases) were assessed for methylation of the marker regions ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671 (GynTect® assay) comparing the 7500 QPCR system (Life Technologies; Thermo Science) routinely used for the assay with the COBAS Z480 QPCR system (Roche Diagnostics).

References

Analyses are still ongoing and will be finished before the meeting. In a smaller evaluation set of samples (n=87), the 100% sensitivity for cancer cases (n=5) could be confirmed and a quite good specificity (CIN3+) of 74% was achieved. False positive rate in PapI, HPV negative samples was 2% (1 out of 43). Overall, the concordance between the two systems in this subset was 90%.

The newly established PCR protocol for the COBAS Z480 QPCR system seems to allow the performance of the GynTect assay with an accuracy comparable to the

original protocol run on the 7500 QPCR system. Analysis of the whole dataset will be presented at the meeting.

00468

GENOME-WIDE DNA METHYLATION PROFILING IDENTIFIES TWO NOVEL METHYLATED GENES TO PREDICT PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

16. Methylation

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Background / Objectives

DNA methylation analysis is a promising approach to complement information on human papillomavirus genotyping in discriminating risk of progression along the continuum of cervical intraepithelial neoplasia (CIN) grades and cervical cancer. We used a pan-epigenomic approach to identify new methylation markers that discriminate among CIN grades, evaluated the correlation between methylation levels and lesion grade, and developed algorithms for risk prediction.

Results

The Methylation Analysis Revealing Key Epigenetic Regulation (MARKER) study comprised 186 physician-collected cervical samples (54 normal, 50 CIN1, 40 CIN2, and 42 CIN3) randomly selected from 643 women referred for evaluation of abnormal cytology at a single-center colposcopy clinic. Extracted DNA was subjected to Illumina Infinium EPIC array analysis. Raw data were analyzed using the ChAMP package in R; applying normalization with BMIQ and batch effect correction for technical replication with ComBat. We implemented the LIMMA package to calculate the p-value for differential methylation using a multiple linear regression model. We performed Spearman correlation analysis (Hmisc package) to determine whether DNA methylation changes correlate with progression. We assessed CpG sites whose state of methylation correlates with lesion grade by generating methylation index cutoff values and a weighted DNA methylation score, comparing normal to CIN3. Methylation markers were assessed via receiver-operating characteristic (ROC) curves for sensitivity and specificity as a function of methylation. Validation of the

identified genes was performed using an independent dataset of women with cervical cancer (GSE68339, n=270).

Conclusion

Our analyses revealed 7715 CpG sites whose DNA methylation level correlated with progression (from normal to CIN1, CIN2, and CIN3). There was a significant trend of increased methylation with disease grade. We identified a bigenic (hyaluronan synthase 1, HAS1 and ATPase phospholipid transporting 10A, ATP10A) methylation marker set; r=0.55, p<0.0001. ROC curve analysis demonstrated that the sensitivity and specificity were both 1.00 for detection of cancer, with independent validation revealing a significant positive correlation (r=0.88, p<0.0001).

References

Genome-wide DNA methylation profiling identified a potentially useful 2-gene methylation cancer prognostic marker. Further exploration of these methylated host genes to improve risk stratification in cervical screening is warranted.

00472

DNA METHYLATION TEST TO DETECT CERVICAL PRE-CANCER IN SELF-COLLECTED VAGINAL AND URINE SPECIMENS.

16. Methylation

B. Nedjai [1], M. Kleeman [1], C. Reuter [1], T. Hollingworth [1], L. Cadman [1], J. Austin [1], D. Patel [1], A. Parberry [2], L. Ashdown-Barr [1], J. Cuzick [1], L. Lorincz [1]

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Background / Objectives

Implementation of HPV testing as a primary screen is becoming the norm worldwide. HPV testing is a very sensitive method but not sufficiently specific, thus the choice of an appropriate triage strategy for hrHPV positive women is key. Clinician-taken samples are the gold standard but self-sampling may be a useful alternative for women unable or unwilling to undergo examination. Collection of urine samples offers another simple option, although the sensitivity of detecting CIN2+ by HPV DNA testing of urine is slightly lower than clinician-taken cervical samples (88.3% vs 94.5%; Cuzick et al., 2017). We developed a triage classifier (S5) for the detection of CIN2+, based on DNA methylation of HPV16, HPV18, HPV31 and HPV33, combined with the human gene EPB41L3 (Brentnall et al., 2015). Our goal was to assess the performance of S5 for detecting CIN2+ using both self-collected vaginal samples and urine.

Results

Women attending the colposcopy clinic at The Royal London Hospital as a consequence of abnormal screening cytology and/or a positive HPV result were recruited as part of the ‘Self-sampling for vaginal HPV: Predictors 5.1’ study. 503 women provided a first-flow urine sample using the Colli-Pee™ device with UCM storage buffer, of which 300 women provided self-collected vaginal samples using a flocked swab (Copan) re-suspended in PreservCyt. DNA was extracted and bisulfite converted, followed by pyrosequencing for S5. Average methylation was calculated for each component biomarker and the S5 score calculated.

Conclusion

S5 showed a highly significant separation between <CIN2 and CIN2+ for both urine and vaginal self-samples ($p<0.0001$). The area under the ROC curve was 0.73 (95%CI: 0.67 to 0.78, $p<0.0001$) for urine samples and 0.74 (95%CI: 0.67 to 0.81, $p<0.0001$) for vaginal self-samples. At the S5 pre-defined cut-off (0.8) sensitivity for CIN2+ in urine samples was 66% with specificity 72%, while for vaginal self-samples they were 71% and 68% respectively.

References

Our study in a colposcopy clinic shows that S5 is promising for testing of self-collected urine and vaginal samples to correctly identify most women with CIN2+. Self-sampling can have a big benefit for women in low and middle-income countries with limited access to effective screening and also for non-attendees in high income countries.

References

Cuzick J et al. 2017; Cancer Epidemiol Biomark Prev 26:1053. Brentnall A et al. 2015; Cancer Biomark 15:669.

00486

VALIDATION OF A DNA METHYLATION CLASSIFIER FOR PREDICTION OF CERVICAL PRE-CANCER IN THE MEXICAN FRIDA POPULATION-BASED HPV SCREENING STUDY

16. Methylation

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Background / Objectives

DNA methylation plays an important role in carcinogenesis and can be the basis of diagnostic and prognostic assays. We evaluated the clinical performance of the S5 DNA methylation score developed in the UK, combining methylation levels of HPV16, HPV18, HPV31, HPV33 and the tumour suppressor gene EPB41L3, as a predictive classifier of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) in hrHPV-positive Mexican women.

Results

A nested case–control analysis from within the large population-based FRIDA screening cohort (ClinicalTrials.gov NCT02510027), focusing on hrHPV-positive women aged 30 to 64 years, with either positive cytology or HPV genotypes 16 or 18. Cases (CIN2+, n=79) were age-matched to controls (n=237) without CIN2+. DNA from exfoliated cervical cells was extracted, bisulfite converted, and amplified for S5 targets; methylation was quantified at specific CpG sites by pyrosequencing. The sensitivity, specificity, and predictive values of the S5 classifier were evaluated. A new proposed S5 cutoff of 3.75 for Mexico was selected by receiver operating characteristic (ROC) curve analyses.

Conclusion

S5 separated CIN2+ from CIN1/normal with an area under the ROC curve (AUC) of 0.75 (95% confidence interval: 0.69-0.82) while the AUC for CIN3+ was 0.81 (95%CI: 0.74-0.89). All 3 invasive cancers were detected and sensitivity for CIN2+ was 64.0% (95% CI 50.4–72.7%), with a specificity of 73.0% (95% CI 66.9–78.5%) and positive predictive value of 43.4% (95%CI: 34.0–53.0%). In comparison, the sensitivity and specificity of HPV16/18 genotyping was 67.1% (95% CI: 55.6-77.3%), and 26.6% (95% CI 21.1-32.7%), respectively, while PPV was 23.3% (95%CI: 18.0-29.4%). The S5 sensitivity and specificity for CIN3+ were 70.3% (95% CI 57.6-81.8) and 76.6% (95% CI 70.7-81.9 %), respectively

References

S5 may be useful as a new triage test for hrHPV-positive Mexican women with CIN2+ requiring referral for colposcopy. Our study confirms an earlier validation in a screening study of European women. S5 is a quantitative assay and various cut-offs can be selected and validated to suit different countries and test settings.

FC 18. Vaccines 5

00187

WHAT IS THE DIFFERENCE IN RISK BETWEEN UNVACCINATED AND VACCINATED WOMEN AGAINST HUMAN PAPILLOMAVIRUS

09. HPV screening

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Background / Objectives

Internationally, Human Papillomavirus (HPV) vaccination uptake in young girls is 30-80%. Will it be reasonable to screen – for cervical cancer - vaccinated and unvaccinated women alike? Next to feasibility issues, this depends on the difference in cervical cancer risk between the two groups. The risk in unvaccinated women will be depend on herd immunity, and thus on vaccination coverage and time since vaccination started. How much herd immunity is expected and when?

Results

We compared three HPV transmission models as part of the Cancer Intervention and Surveillance Modeling Network (CISNET) on predicted HPV16/18 infection incidence reduction and resulting herd immunity effect, assuming vaccination with 60% coverage. Herd immunity effect is defined as the cervical cancer incidence reduction in non-vaccinated women relative to vaccinated women (100% means cervical cancer risk is equal in unvaccinated and vaccinated women).

Conclusion

In the steady state, HPV16 incidence reduction was predicted to be 80, 73 and 65% in all women for the three independent models. This was reached after 70, 69 and 37

years respectively. For HPV18 the results were similar. The corresponding herd immunity effects were 56, 32 and 17% respectively.

References

Although herd immunity is important for decisions concerning cervical cancer screening, there seems to be uncertainty about its expected magnitude and the rate at which it will develop. Monitoring of the HPV prevalence, especially in unvaccinated women, in various populations, combined with comparative modeling, will add to the understanding of the dynamics of herd immunity and improve further projections.

00139

DECLINES IN ANOGENITAL WARTS DIAGNOSES SINCE THE CHANGE IN 2012 TO USE THE QUADRIVALENT HPV VACCINE IN ENGLAND: DATA TO END 2017

29. Genital warts

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Background / Objectives

In 2008, a national human papillomavirus (HPV) vaccination programme to prevent cervical cancer was introduced in England using the bivalent vaccine (HPV types 16 and 18 only). In 2012, the programme changed to offer the quadrivalent vaccine that additionally protects against the two HPV types that cause the majority of anogenital warts (AGW; HPV6 and 11). Coverage for the vaccination programme has been high, with over 85% of routine cohorts (12-13 year olds) completing the recommended schedule. We present data reporting AGW diagnoses in specialist Sexual Health Clinics (SHC) in England to the end of 2017, including diagnoses up to 17 years of age among birth cohorts offered routine vaccination with the quadrivalent vaccine.

Results

Data were obtained from the GUMCAD STI Surveillance System (GUMCAD), submitted by SHC, for years 2009-2017. This surveillance system includes data on all attendances and diagnoses at SHC in England. Records coded as first episode AGW for females, heterosexual males, and men who have sex with men (MSM) aged 15-17 years old were extracted. The incidence of AGW diagnoses per 100,000 population was calculated using national population estimates by sex and age, and the percentage of men who have sex with men (based on data published in the Natsal-3 study of sexual attitudes and lifestyles in the UK). Percent declines in the rates of AGW diagnoses were calculated between 2014 and 2017, during which most females aged 15-17 years would have been offered the quadrivalent vaccine. Poisson regression was used to test for trends over time for each sub-group.

Conclusion

Between 2014 and 2017, there were substantial declines in the incidence of AGW diagnoses in SHC among young females aged 15-17 years, from 257.5 per 100,000 population in 2014 to 45.7 per 100,000 population in 2017 (82.3% decline, p-value for trend <0.001). Declines in the incidence of AGW diagnoses were also seen among same aged heterosexual males (67.7% lower in 2017 than 2014 in 15-17 year old heterosexual males, p-value for trend <0.001). Reductions in AGW diagnoses in MSM aged 15-17 years were less clear (decreased by 13.6%, from 129.9 in 2014 to 112.2 in 2017 per 100,000 population, p-value for trend 0.219).

References

Substantial declines in AGW diagnoses have been seen in young females who would have been offered the quadrivalent vaccine as part of the national HPV vaccination programme, as well as among same aged heterosexual males, strongly suggesting a herd protective effect. Weaker declines were also observed in young MSM. Surveillance plans are in place to continue to monitor AGW diagnoses to evaluate the impact of both female and targeted MSM HPV vaccination.

00328

EXTINCTION OF HPV 6 AND GENITAL WARTS IN A POPULATION WITH SUBOPTIMAL HPV VACCINE COVERAGE

29. Genital warts

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Background / Objectives

The vaccination of HPV naive women against HPV 6/11 protects sufficiently from genital warts and may even lead to protection of non-vaccinated men and women in the same population (via herd protection).Howeover, it is uncertain what level of vaccine coverage we require for such cohort effects.

Results

WOLVES (Wolfsburg HPV epidemiological study) invited to participate all women born 1983/84, 1988/89 and 1993/94 with first residency in Wolfsburg. The participants received annual visits with HC2-HPV testing and genotyping with SPF-10 PCR of all positive and 10% of HC2 negative samples.

Conclusion

Between Oct 2009 and Jan 2018 2477 women were included. The HPV vaccination coverage rate rose from 6.1% to 18.4% among 26 years old women. The corresponding rates for 21 years old women increased from 23.7% to 48.7%. Simultaneously the life risk to suffer from at least one episode of genital warts before age 27 dropped from 4.7% to 2.5%. The disappearance of genital warts was underlined by a decline in the prevalence of HPV 6 from 2.1% to 0.2% among 26 years old women and from 2.0% to 0.0% among 21 years old women in our population.

References

WOLVES is the first real- life study population (not exclusive data base analysis) to look at the impact of HPV vaccination under other on genital warts prevalence and HPV 6 incidence in Germany. We observed the unexpected decline of genital warts

and complete disappearance of HPV 6 in a population with suboptimal HPV vaccine coverage.

00148

PUBLIC HEALTH AND ECONOMIC IMPACT OF HPV VACCINATION IN THE PORTUGUESE NATIONAL IMMUNIZATION PROGRAM

36. Public health

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Background / Objectives

In Portugal, HPV vaccination was included into the National Immunization Program (NIP) for 13-years girls in 2008 using the 4-valent HPV (4vHPV) vaccine. In 2017 the 4vHPV vaccine was replaced by 9-valent HPV (9vHPV) vaccine and the age for vaccination was anticipated for 10 years. The aims are: (i) to assess the public health and economic impact of the first 10 years of HPV vaccination in the NIP; (ii) to estimate the impact for the upcoming years. An additional scenario considering gender neutral vaccination with 9vHPV vaccine was run.

Results

A published HPV disease transmission dynamic model accounting for herd protection effects with a lifetime horizon (100 years) has been adapted and calibrated for Portugal. The model considered the occurrence of cervical intraepithelial neoplasia (CIN), cervical, vaginal, vulvar and anal cancers; and also penile and oropharyngeal cancers. Demographic inputs were obtained from Statistics Portugal and annual all-cause mortality rates were extracted from the Portuguese Mortality table 2014-2016. Costs were taken from Santana et al[1] study and Decree 207/2017.

Conclusion

The first 10 years of HPV vaccination in NIP resulted in the reduction of CIN 1, CIN 2/3 and genital warts incidence (11,465 events avoided) and savings of €4,914,150. The maintenance of the current program for next 90 years will result in the avoidance of 1,437,091 events (e.g., cervical, vaginal, vulvar, anal, oropharyngeal cancers, CIN

1, CIN 2/3 and genital warts) and potential savings of €1,148,292,188. The implementation of universal vaccination program using the 9vHPV vaccine (boys and girls aged 10 years) will significantly reduce the clinical and economic burden resulting in 1,788,610 events avoided and savings of €1,329,629,689) compared to cervical cancer screening only.

References

The first 10 years of HPV vaccine in NIP resulted in additional benefits for the Portuguese Public Health, which become greater as time progresses. Notwithstanding, the reduction of the burden and expenditure related to HPV-related diseases can be amplified by the implementation of a 9vHPV universal vaccination program.

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00273

TYPE-SPECIFIC HUMAN PAPILLOMAVIRUS PREVALENCE IN THE NORTH OF MEXICO, A 10 YEAR STUDY AND RELATION WITH HPV VACCINE COVERAGE

36. Public health

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Background / Objectives

Cervical cancer is the second cause of death worldwide, and still the leading cause of death from cancer in Mexico. Human Papillomavirus(HPV) is the main cause of cervical cancer. Prevalence of cervical HPV infection varies worldwide and data regarding HPV prevalence and genotypes in Mexico is still limited. Detection and genotyping of HPV is an essential tool for screening, diagnosis, and management of HPV-related cervical cancer and its precursor lesions. The purpose of this study was to find data on prevalences of HPV genotypes, and prevalence of infections with multiple HPV genotypes in our population to improve specific prevention and management activities.

Results

This research was done at IMIGO (Instituto Mexicano de Infectologia, Ginecoologia y Obstericia) in Monterrey Mexico, with the database from our patiens from year 2008 to 2018. The kits used for typification were Innolippa HPV Genotyping Extra I and II, Linear Array HPV Genotyping Test, Seeplex HPV 18 ASE DPO and Abbot Real Time all processed at the Molecular Diagnosis Unit of the Hospital Universitario U.A.N.L. in Monterrey Mexico. The inclusion criteria were as follows: women and men with a history of sexual activity with risk of HPV infection, patients with positive HPV infection, and patients requesting an HPV test. We obtained 816 samples: 524 positive and 292 negative for HPV infection.

Conclusion

In our 524 positive samples, a total of 957 different HPV viruses were isolated.The most prevalent HR HPV serotypes found are HPV-16 (8.78%), HPV-51 (8.67%), HPV-52 (7.84%), HPV-33 (7.75%), HPV-31(5.54%), and LR most prevalent

was HPV-6 (6.79%). Overall 56.2% are HR HPVs, 11.7% probably HR, 28.5% are LR and only 3.55% of the virus could´t be typified by our test kits. In the 524 positives samples we found that 56% had mono-infections and 44% had multiple infections as high in some cases as 8 diferent serotypes in one patient(. Specifically 26.5% had multiple HPV infection with 2 serotypes, 9.92% with 3 serotypes, 4.01% with 4 serotypes, 2.1% with 5 serotypes and 1.15% with 6 serotypes .

References

HPV prevalence in our population was high 64%, with more than 56% having HR serotypes and up to 44% having multiple infections. We found that from the top 6 most prevalent virus found in our study were 5 HR and 1 LR and from those 5 are included in the HPV9 vaccine, confirming a strategic increased benefit over the other vaccines available in reducing the risk of cancers caused by HPV in our country.

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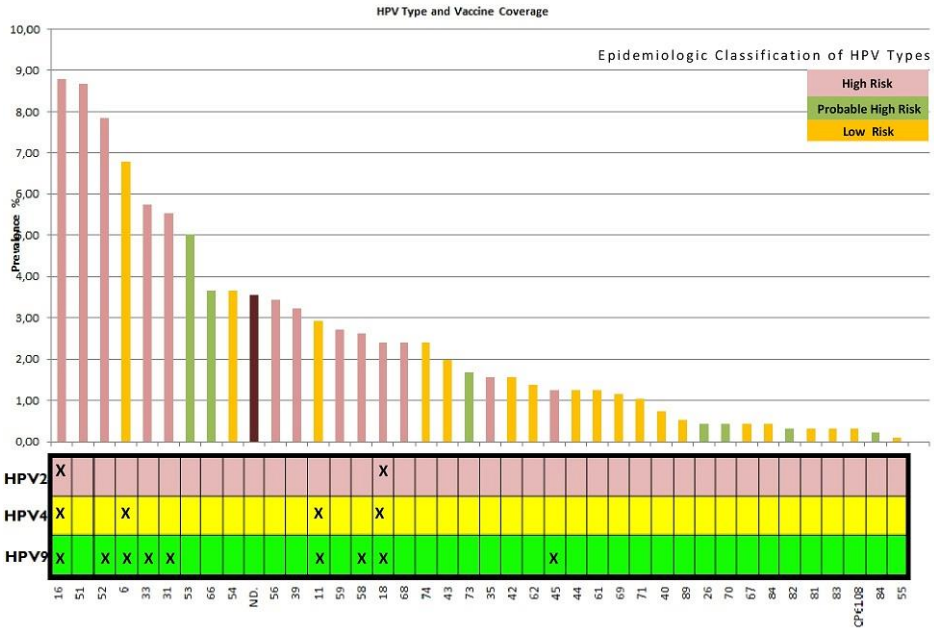
HPV Type and Vaccine Coverage
Epidemiologic Classification of HPV Types
High Risk
Probable High Risk
Low Risk
Prevalence %
10,00
9,00
8,00
7,00
6,00
5,00
4,00
3,00
2,00
1,00
0,00
HPV2
HPV4
HPV9
16 51 52 6 33 31 53 66 54 ND. 56 39 11 59 58 18 68 74 43 73 35 42 62 45 44 61 69 71 40 89 26 70 67 84 82 81 83 CP6108 84 55

00274

HPV SEROPREVALENCE AND GENITAL HPV INFECTIONS IN A COHORT OF YOUNG WOMEN IN THE NETHERLANDS SEVEN YEARS POST-VACCINATION

36. Public health

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Background / Objectives

HPV vaccination is effective against persistent infections and induces a robust serological response. However, many questions remain about vaccine induced or naturally derived antibodies and their role in protection. Therefore, we aim to describe the immunogenicity of the bivalent vaccine in a population-based setting up to seven years (7y) post-vaccination and to explore the longitudinal relation between HPV DNA presence and humoral response against HPV among vaccinated.

Results

A prospective cohort study including 1151 girls (birth cohort 1993) who were eligible for the catch up campaign in 2009 was performed in the Netherlands. One month prior to vaccination and each consecutive year post vaccination a vaginal self-swab, a serum sample, and a questionnaire were collected. A VLP-based multiplex immunoassay (MIA) was used to measure type specific HPV antibodies against HPV16, 18, 31, 33, 45, 52 and 58. The HPV-DEIA-LiPA25 could detect twenty-five HPV DNA genotypes including the high-risk types from the MIA. Type specific geometric mean concentrations (GMC) of serum IgG and seroprevalences were calculated (cut-offs described in (1)). We explored the association between IgG and incident infection in the subsequent round in a multilevel linear model.

Conclusion

1038 participants with baseline measurement were included (71.7% vaccinated). GMCs against vaccine types HPV16/18 peaked after vaccination and remained high up to 7y post-vaccination (seroprevalence 99-100% in vaccinated vs. 10-18% in unvaccinated 7y post-vaccination). GMCs against cross protective types HPV31/45

were lower, but still significantly higher than in unvaccinated individuals (GMC ratio 7y post-vaccination HPV31: 13.7, 95%C.I. 11.0-17.1, HPV45: 9.8, 95%C.I. 7.9-12.2). The association between IgG and incident infection in the subsequent round in vaccinated showed higher GMCs in uninfected participants compared to those with an HPV infection for HPV16 (GMC ratio 2.1, 95% C.I. 0.5-9.7), HPV31 (1.3, 95%C.I. 0.6-3.0), HPV45 (1.8, 95%C.I. 0.4-8.1). However, the opposite was seen for HPV18 (0.6 95%C.I. 0.1-3.1).

References

Serum IgG antibody responses against vaccine types remain high up to 7y post-vaccination in a population based setting. No significant association was found between type specific IgG and incident infection in the subsequent round , although vaccinated individuals with break-through infections showed slightly lower antibody levels one year before the infection. Still, this effect was not observed for all HPV types, providing no clear indication for the role of serum antibodies in protection against infection. The association between antibodies and infection at other time points will be explored further.

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00453

IMPACT OF A SINGLE-COHORT HPV VACCINATION STRATEGY WITH QUADRIVALENT VACCINE IN NORTHEAST SPAIN: POPULATION-BASED ANALYSIS OF GENITAL WARTS IN MEN AND WOMEN

36. Public health

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Background / Objectives

Catalonia, a region of 7.5 million inhabitants in northeast Spain, started in 2008 a school-based, single-cohort HPV vaccination programme targeting 11-year-old girls and offering the quadrivalent HPV vaccine free of charge, except for the year 2010 when the bivalent HPV vaccine was used. Throughout the observation period coverages have been steadily over 80%. Vaccine coverage for non-eligible cohorts is estimated to be very low. We aimed to estimate the population impact of a female single-cohort HPV vaccination programme through analysis of trends in genital warts (GW) diagnoses in a high coverage scenario.

Results

Data were obtained from the Information System for Research in Primary Care (SIDIAP), a population-based database of anonymised electronic health records that includes information of approximately 5.6 million patients (74% of Catalonian population). We retrieved all records of new GW diagnosed between 2009-2016 and for comparison purposes all new diagnoses of genital herpes and other STI were also collected. Annual incidence rates were calculated stratified by age and sex using joinpoint regression to estimate trends and annual percentage changes (APC). The first vaccinated cohort (girls born in 1997) turned 19 in 2016, the end of the study period.

Conclusion

GW incidence among women aged 16 to 19 years decreased a 61% from 2012 to 2016 (APC -19.4; 95% CI: -30.0%- -7.3%). In contrast, the incidence of genital herpes in same-aged women increased throughout the study period (APC 11.1; 95% CI: 7.2%-15.2%) and GW presented with increasing trends for the rest of age groups until age 60. Among men aged 20 to 22 years, the increasing incidence of GW shifted to a downward trend in 2013 (APC 2009-2013: 17.0; 95% CI: 8.2%-26.5%; and APC 2013-2016: -4.5%; 95% CI: -14.6%-6.9%). A similar pattern was observed among men aged 23 to 25 years, in which the incidence shifted to a decline in 2014 (APC 2009-2014: 16.0; 95% CI: 12.0%-20.2%; and APC 2014-2016: -6.0%; 95% CI: -18.4%-8.3%). As opposed to GW, in men aged 20 to 25 years the incidence of genital herpes increased significantly over the study period.

References

In our study population, GW have substantially decreased among vaccinated cohorts and there is a shift to a downward trend in young men. A high coverage of a single-cohort HPV vaccination strategy has provided extended benefits through a herd effect of HPV vaccination in non-vaccinated men.

FC 19. Diagnostics & management 2

00427

A NOVEL PATCH SAMPLING APPROACH FOR GRADING & LOCATING CERVICAL LESIONS

19. New technologies

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Background / Objectives

Screening for cervical cancer and its precursors can be facilitated by the detection of HPV DNA. Multiple studies have demonstrated the higher sensitivity of this approach to HSIL. However primary HPV screening has low specificity on its own thus leading to an increase in the number of women that are referred to colposcopy with LSIL. This stems from the fact that mere presence of DNA doesn't correspond to malignant disease. Furthermore, an increase in referrals to a subjective procedure like colposcopy may lead to unnecessary treatment, increasing the risk of neonatal complications due to prematurity.

Results

We utilise a novel patch sampling approach to obtain the surface cells of the cervix (including the transformation zone), while preserving their spatial positions. Patients attending colposcopy had a pre and post-acetic acid application photo, interspersed by patch sampling. 25 patients with a high-grade smear (at time of sampling) and then histology proven HSIL were recruited in one arm vs. 25 patients with LSIL. This patch is then probed with antibodies to the E4 protein (LSIL marker) and p16/MCM (HSIL). The signal for each antibody is then analysed using a mathematical model/ image analysis approach to identify these regions in sheets of cells collected on the patch.

Conclusion

Our novel approach safely samples the cells at the surface of the cervix and can be probed with biomarkers. Our analysis approach is able to identify clusters of cells that are p16/MCM positive, indicating the presence of underlying HSIL, while E4 clusters indicated the presence of underlying LSIL. We were then able to successfully quantify the signal which, correlated with the underlying histological diagnosis. This approach has also been successfully automated thus reducing any operator related

bias that affects current methods. Our approach is also less invasive (compared to cytology) making it more acceptable to women and thus may lead to improved uptake. Finally turnaround time for our approach is only 36 hours, which would enable focusing of resources on women that truly require treatment.

References

Our novel approach of applying biomarkers with preservation of spatial information to localise HPV mediated cervical disease has proven effective in identifying HSIL. Furthermore, the use of this in combination with E4 enables us to quantitatively discriminate HSIL vs. LSIL. Thus, in the context of primary HPV screening this approach has the potential to prevent unnecessary referrals to secondary care. Our non-invasive patch sampling approach has the added potential to be used to monitor patients over time, especially those with CIN2 diagnosis', without the need for multiple, invasive procedures. Finally, the ability to localise lesions has the potential to lead to more personalised treatments.

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00601

Assisted Digital Cervicography (ADC): A New Tool for Clinical Screening of the Cervix

19. New technologies

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Background / Objectives

Methods of cervical cancer screening differ, but include screening through cytology (PAP), Human Papillomavirus (HPV) testing, naked-eye visualization with acetic acid (VIA) or visualization with lugols iodine (VILI), or a combination of these methods. However, no one method of screening is enough to definitively eliminate risk for the development of CIN. 40 studies compared HPV to cytology on over 140,000 women between 20 to 70 years old who attended routine cervical screening. For every 1,000 women screened, there will be 980 women who will not have precancerous changes.[i] However, among the 980 normal women, there are many infections and/or abnormalities that can be found on the cervix visually that may increase the risk of CIN development if the infection remains untreated through increased risk for HPV entry. These infections may not be found on a cytology or HPV test. Identifying these infections is important because a transient period of HPV may begin to replicate in immature metaplasia and/or other infections that can specifically be seen through a visual exam. Viral replication may induce the host cells to proliferate abnormally, potentially leading to CIN.

Results

A digital colposcope was used at the primary clinical screening, alongside cytology and HPV tests to investigate the number of such infections that exist among a normal screening population.

Conclusion

Among the first 100 patients screened with assisted digital cervicography (ADC) during a routine, primary clinical exam in Tel Aviv findings show 15 cases of normal cervixes, 31 cases of normal metaplasia, 24 cases of immature metaplasia, 26 cases of miscellaneous infections, and 4 cases of potential CIN.

References

A new clinical approach called ADC can be adopted, where a digital colposcope is used at the primary clinical screening, alongside cytology and HPV test, where the clinician uses the colposcopic lightsource and magnification, alongside acetic acid and lugol's iodine to visually identify these types of viral infections that can lead to viral replication, and entrance of HPV. The technique is affordable and easy to conduct by general gynecologists who do not need to be colposcopy experts after completing a short, online course. Integrated into the digital colposcope is a system to consult with an expert or tutor so that the patient does not need to have a referral or travel far for routine exams for non-invasive findings. This is a tool to learn the physiopathology of the cervix and to treat benign lesions in order to prevent HPV entry. This also leads to a decrease in stress and anxiety among patients that are simply undergoing routine examination and treatment. This is a new era of clinical screening to prevent CIN development and improve patient care.

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00006

EVIDENCE FOR CLINICAL UTILITY OF EXTENDED HPV GENOTYPING IN PERSISTENCE TRACKING AND FOLLOW-UP AFTER ABNORMAL RESULTS AND COLPOSCOPY AND TEST-OF-CURE

20. Diagnostic procedures / management

J. Andrews

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Background / Objectives

Guideline originators have not yet included an analysis of the body of science published recently about the clinical value of extended HPV genotyping (xGT) in persistence tracking, follow-up of women with abnormal results, and follow-up after treatment of high-grade cervical intraepithelial neoplasia (CIN).

Results

PubMed, Cochrane Database of Systematic Reviews, and Health Technology Assessment database were searched from 2001 through 2018 for relevant studies. Hand-searching of retrieved article reference lists supplemented the search. Eligible studies included prospective studies of women and retrospective studies of residual specimens from women that were tested using HPV genotyping tests following an abnormal screening result, or colposcopy, or treatment for high-grade cervical intraepithelial neoplasia. The reference standards were CIN2 or CIN3 or CIN2+ or CIN3+ or invasive cervical cancer. The timeframe for follow-up studies was at least 6-months to determine persistence; periods of 12-months and 24-months were accepted. This systematic review has been registered with PROSPERO. Cochrane risk of bias assessment was performed. GRADE methodology was used to establish quality and strength of evidence.

Conclusion

A PRISMA flow diagram is presented for this systematic review. 31 original research articles met inclusion and exclusion criteria. Reporting xGT results provides profound discrimination of both current and future CIN3+ risks, due to the differential risks of same genotype persistence versus new genotype infection. Within subjects with persistent same genotype, xGT can discriminate risk by more than ten-fold. xGT

could be utilized as follow-up type-specific persistence versus clearance, to support risk-based clinical decisions. Similar management for similar risk-discrimination is benchmarked.

References

Based on quality-evaluated studies that met inclusion criteria, xGT appears very promising as follow-up of persistence versus clearance, to discriminate risk and support risk-based clinical action steps by the principle of equal management for equal risk. The role of same genotype persistence is critical to test of cure assessments. Models for different management paradigms are described. The information in this report is intended to help guideline panels, policymakers, clinicians, and women make informed decisions about the selection of health care services, is intended as a reference, and not as a substitute for clinical judgment.

References

Note: the author/presenter is a former associate professor of Ob/Gyn, Editor-in-Chief of a peer-reviewed journal; Cochrane reviewer; Senior Scientist in an Evidence-based Practice Center; and current member of GRADE

00028

Sexual Function of Women is not impared by HPV related lesions

20. Diagnostic procedures / management

S. Fornage

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Background / Objectives

While the stressful psychological impact of lesions associated to Human Papillomavirus (HPV) and their diagnosis in women is well known, evidences of their sexual impact are lacking. Our aim is to evaluate the impact of HPV related lesions on the female sexual function with validated questionnaires. Our first outcome was to determine if there was a differences in the FSFI global score and sub-scores between the two populations. Our second outcome was to determine the chararcteristics of female sexual dysfunctions in women with HPV-related lesions.

Results

This is a prospective study comparing the sexual function of women diagnosed for the first time with an abnormal cervical PAP smear or vulvar condyloma (case group) to the sexual function of women with a normal cervical PAP smear (control group) . We used 2 validated questionnaires, the Female Sexual Function Index (FSFI) and the Hospital Anxiety Depression Scale (HADS) mailed to the patients. We excluded women younger than 21 as well as menopausal women and pregnant women.

Conclusion

Forty-eight patients in both groups returned the questionnaires. Populations significantly differ in age, smoking habit, parity and gestity, use of hormonal contraception and vaccination against HPV. Mean FSFI total score is similar in the case group (29.1) and in the control group (28.8) (p=0.3). FSFI scores is <26.55 in 44.4% of the patients of the case group and in 55.6% of the patient of the control group. These differences are not statistically significant. Amongst the FSFI items, arousal score is significantly better in the case group. The others subscores are similar. HADS scores are also similar between the 2 groups.

References

Unlike our clinical experience, global female sexual function is not impared by HPV related lesions. This call into question the choice of the questionnaires and more globally the quantitative approach for evaluation of the female sexual function. Arousal is better in the case group and this difference has to be further studied. We propose the add qualitative studies to further explore the female sexual function in patients with HPV related lesions.

00217

Risk factors for positive margins in transformation zone excision specimens

20. Diagnostic procedures / management

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Background / Objectives

Approximately 10-30% of high-grade squamous intraepithelial lesions (HSIL) of the uterine cervix progress to invasive disease. Transformation zone excision (TZE) effectively reduces the risk of progression. Incomplete excision is associated with higher rates of residual and recurrent lesions.

The aim of this work is to identify risk factors associated with positive margins (HSIL) in TZE specimens.

Results

Retrospective review of the records of patients submitted to TZE, and who had a diagnosis of HSIL in the surgical specimen (2011 to 2018).

Conclusion

Out of 201 patients, 28 had positive margins (13.9%). The endocervix was involved in 60.7% (17/28) of these, while the exocervix was in 21.4% (6/28), and both endo/exocervix in 17.9% (5/28).

Women with positive margins were older (mean age 44.5±14.8 vs. 38.9 ± 9.4 years, $p<0.05$) and were more likely to be postmenopausal [29.03% (9/31) vs. 11.46% (18/157), $p<0.01$].

No differences were found concerning immunosuppression, smoking, previous vaccination against human papillomavirus (HPV), or type of contraception.

Non full visualization of the squamocolumnar junction (SCJ) at colposcopy was associated with positive margins [30.95% (13/42) vs. 8.40% (10/119), $p< 0.01$). If the transformation zone (TZ) was completely endocervical, regardless of visualization or

not of the SCJ, there was also a trend to have positive margins [28.57% (6/21) vs. 13.46% (7/52) if only partially endocervical and 8.86% (7/79) if totally in the exocervix, p=0.059].

Margin status was not associated with the TZ dimensions, location of the lesions, or number of quadrants affected.

No differences were observed when comparing the technique used to perform the TZE (loop vs. needle electrocautery excision) nor with the volume of the specimen.

Higher grade cytologic abnormalities were more frequently associated with positive margins: ASC-H/HSIL 17.29% (23/133) vs. LSIL 2.85% (1/35), p<0,05. On the other hand, HPV genotype was not an independent predictor of margins status.

As the severity of lesions increased, so did the rate of positive margins: CIN2 11.01% (4/73), CIN3/CIS 15.52% (18/116) and invasive carcinoma 66.77% (6/9), p<0.01.

References

Older age, menopausal status, incomplete visualization of the SCJ, ASC-H/HSIL Pap smear, and more severe histology were associated with positive margins in TZE specimens.

No differences were found concerning the dimensions of the specimens obtained.

Contrarily to what has been reported by others, HPV16 was not associated with a higher incidence of positive margins.

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Positive margin status in uterine cervix cone specimens is associated with persistent/recurrent high-grade dysplasia. Shaco-Levy R.; *et al*. Int J Gynecol Pathol. 2014 Jan;33(1):83-8

00293

HUMAN PAPILLOMAVIRUS AND MEDICALLY ASSISTED REPRODUCTION: A MULTICENTER PROSPECTIVE STUDY

20. Diagnostic procedures / management

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Background / Objectives

Despite Human Papillomavirus (HPV) is one of the main causal agents of sexually-transmitted diseases, no recommendations exist on the risk related to HPV during Assisted Reproductive Technology (ART) procedures. The main objective of this prospective multicentric cohort study was to evaluate the prevalence of HPV at the different steps of ART program. Secondary objectives were to investigate (1) the efficiency of sperm pellet preparation procedures to eliminate HPV, (2) the correlation between HPV detection in semen and male infertility, and (3) the correlation between HPV detection in males and/or females and success of life birth rate.

Results

A total of 914 consenting couples enrolled in a ART program in Saint-Etienne and Bordeaux University Hospitals was included in the study between 2012 and 2016. Genital HPV screening was performed in males and females using a real-time PCR protocol derived from the INNO-LiPA® HPV Genotyping Extra II assay (Fujirebio) [1]. HPV DNA testing was carried out at the different steps of ART for couples detected positive for HPV, and for newborns in case of pregnancy.

Conclusion

The prevalence of HPV DNA was 17.1% in semen (15.8% in seminal plasma only, 0.7% in the final sperm fraction only and 0.6% in both) and 16.1% in cervicovaginal samples (CVS). The percentages of high-risk genotypes (mainly 31, 39, 51 and 52) were 63.7% and 65% in semen and CVS, respectively. Among HPV positive women enrolled in In Vitro Fertilization program, 26.5% of oocytes punctures and 15.2% of embryos culture media also tested positive for HPV DNA. Four newborns from a total of 253 newborns tested positive for HPV at the throat level, 2 exhibiting similar genotypes as the mother, 1 as the father and the last from parents both negative for HPV. No correlation was found between HPV detection and fertility parameters (in either men or women) or procreation success.

References

Our exhaustive study indicates the presence of HPV DNA of oncogenic genotypes at several steps of ART procedures until child birth. Our findings raise the question of the relevance of a specific management of the risk linked to HPV during ART and of a revision of guidelines in Reproductive Biology Units (in particular the sperm pellet preparation). More broadly, our data may plead in favor of an expansion of HPV vaccination towards males.

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00349

ACCURACY OF COLPOSCOPY AND p16/Ki67 IN THE DETECTION OF HIGH GRADE LESIONS IN HPV-POSITIVE WOMEN

20. Diagnostic procedures / management

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Background / Objectives

The objective of this investigation was to evaluate the accuracy of colposcopy and p16/Ki67 in the detection of high grade disease (HGD), considered CIN 2+, in women with high risk HPV (hrHPV).

Results

Retrospective study of 220 women with positive hrHPV who underwent cervical biopsy in our department, between December/2014 and December/2017. All patients underwent colposcopy.

Conclusion

In our study the mean age was 39,3±10,5 [16-79] years. Cytology results were 20 (9,1%) NILM, 39 (17,7%) ASC-US, 12 (5,5%) ASC-H, 89 (40,5%) L-SIL, 35 (15,9%) H-SIL, 17 (7,7%) AGC and 8 (3,6%) suspicious of carcinoma; 113 (51,3%) were HPV 16 or 18 positive and p16/Ki67 was positive in 138 (62,7%). Colposcopy revealed major abnormal findings in 60,0%. Histological diagnosis after biopsy were: normal in 16 cases (7,2%), 93 (42,3%) CIN1, 68 (30,9%) CIN2, 27 (12,3%) CIN-3 and 9 (4,1%) carcinomas (5 [2,3%] adenocarcinomas and 4 [1,8%] SCC).

Within the group of positive p16/Ki67 there were 85 cases of biopsy-confirmed CIN2+, thereof 30 CIN3+ cases; and only 13 cases of CIN2+ (4 CIN3 cases) within the negative ones. p16/Ki67 showed high sensitivity (86,7%) and modest specificity (55%) in identifying the presence of HGD (CIN2+) at surgical biopsy. Positive and negative predictive values (PPV/NPV) for HGD were 63,4% and 82,2%, respectively

(ROC 0,710). In contrast colposcopy showed 74,8% sensitivity, 52,7% specificity, 59,2% PPV and 69,4% NPV (ROC 0,655). If we consider CIN 3+ lesions the performance of p16/Ki67 and colposcopy was respectively: 91,2% vs. 77,8% sensitivity, 39,7% vs.42,4% specificity, 22,0% vs.20,9% VPP and 95,9% vs. 90,6% NPV.

Making a separate analysis of the performance of p16/Ki67 for CIN2+ between the ASC-US and LSIL we found 86,8% sensitivity, 57,1% specificity and 90,6% NPV (83,3% sensitivity, 76,0% specificity and 90,4% NPV for ASC-US alone and 88,6% sensitivity, 49,2% specificity and 90,6% NPV for LSIL alone). The corresponding results for colposcopy were 77,5% sensitivity, 56,5% specificity and 84,2% NPV for both ASC-US and LSIL (76,9% sensitivity, 57,1% specificity and 80,0% NPV for ASC-US alone and 77,8% sensitivity, 53,3% specificity and 84,2% NPV for LSIL alone).

References

In conclusion double staining showed better performance than colposcopy in predicting HGD, being even better if we consider CIN 3+ lesions. This difference is larger if we consider low grade citologies. As a result it could be a usefull tool as an adjunct to cytology in the triage of hrHPV eventually decreasing the need for colposcopy referrals.

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00384

THE ADDED VALUE OF RESCREENING CYTOLOGY NORMAL SAMPLES WITH POSITIVE HPV MRNA TEST FOR THE DETECTION OF CIN2+ IN PRIMARY SCREENING

20. Diagnostic procedures / management

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Background / Objectives

Objectives. To estimate the increased detection rate of CIN2+ in women with normal Pap-smears by rescreening Pap-smears from HPV mRNA positive samples.

Results

Methods. From April 4th, 2013, the Department of Pathology, Ålesund Hospital, introduced a study by rescreening all normal Pap-smears that had a positive HPV mRNA test (NorChip PreTect SEE) (types 16, 18 and 45) in women younger than 40 years. Within the SymPathy database, a study population of 4 366 women aged 23–39 years with no prior history of CIN1+ was established.

Conclusion

Results. 38% of women with normal cytology were tested via HPV mRNA (1444/3851), and 28 samples were positive (1.9%). After re-evaluation of the index cytology and subsequent follow-up smears, 15 women had colposcopy, resulting in five diagnoses of normal biopsies, 6 CIN1 and 9 CIN2+. The detection rate of CIN2+ among rescreened normal Pap-smears was 0.62% (95% CI: 0.60–0.65). In the ASC-US+ arm (n=515), 138 CIN2+ were detected. If we apply the CIN2+ detection rate among cytology normal / HPV mRNA-positive women (0.62%) to the arm of women with normal cytology without HPV testing, a 17-18% increase in CIN2+ detection rate was estimated. Four cancers were detected in the ASCUS+-arm, none among rescreened SEE-positives.

References

Conclusions. By testing all women with normal cytology with a specific HPV mRNA test, a significant increase in screening program sensitivity can be achieved. The volume of rescreened smears (1.9%) is very low. In addition, the study adds quality to educating the screeners by rescreening presumably false negative Pap-smears.

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00534

LOW PROPORTION OF UNREPORTED CERVICAL TREATMENTS IN THE CANCER REGISTRY OF NORWAY

20. Diagnostic procedures / management

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Background / Objectives

Accurate information about treatment is needed to evaluate cervical cancer prevention efforts. We evaluated reasons of being without recorded cervical treatment in the Cancer Registry of Norway (CRN).

Results

We identified 47 423 (92%) high-grade cervical dysplasia patients with treatment and 3 983 (8%) without treatment in the CRN in 1998–2013. We linked the latter group to the nationwide registry of hospital discharges in 1998–2015. Of patients still without treatment, we selected randomly 375 for review of their medical history. Factors predicting incomplete treatment records were assessed by multiple imputation and logistic regression.

Conclusion

Registry linkage revealed that 10% (401/3 983) of patients received treatment, usually conisation, within one year of their initial high-grade dysplasia diagnosis. 11% (n=44) of those were missing due to unreporting and 89% (n=357) due to misclassification at the CRN. Of all cases in medical review, patients under active surveillance contributed almost 60% (223/375). Other reasons for unregistered treatment were uncertain dysplasia diagnosis, invasive cancer or death. Coding error occurred in 19% (73/375) of randomly selected cases. CRN undercounted receipt of treatment by 38% (n=1 526) among patients without registered treatment which translates into 97% overall completeness of treatment data. Incomplete treatment records were particularly associated with public laboratories, patients aged 40–54 years, and the latest study years. The average annual number of conisations recorded in the CRN has increased from 3,900 in years 2010-2013 to 5,700 in years

2014-2016. This might reflect a decrease in incomplete recording of treatment data and/or true increase in number of conisations nationwide.

References

CRN records close to complete treatment data on cervical treatments, with missingness largely being due to misclassification. Validity of treatment data has been identified as a high-priority task in registry linkage

00188

Can Thin HSIL of the Cervix Progress to Invasion?

22. Cervical neoplasia

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Background / Objectives

Thin high-grade squamous intraepithelial lesions (HSIL) of the cervix are a variant of HSIL that are <9 cells thick (1). Thin HSILs develop in early immature metaplastic squamous epithelium of the transformation zone (TZ) without anteceding low-grade squamous intraepithelial lesions (2). The risk of thin HSIL progressing to invasion is unclear.

Results

We studied 34 consecutive conization specimens containing microinvasive (FIGO stage Ia1) squamous cell carcinoma (SCC) of the cervix.

Conclusion

All early invasive foci were located inside the TZ and arose more often from HSIL in endocervical glands than from HSIL at the ectocervix. Early stromal invasion originated from a field of thick HSIL in 32/34 (94%) specimens, only 2 (6%) specimens showed early stromal invasion originating from a field of thin HSIL of 7-9 cells thickness. No early stromal invasion originated from thin HSIL 4-6 cells thick.

References

Our findings indicate that the risk of invasion of thin HSIL is low, and it may be that women with biopsy-confirmed thin HSIL may be candidates for expectant follow-up. We postulate two latency periods between thin HSIL and microinvasive SCC: the first between thin HSIL and thick HSIL. Epithelial thickening occurs due to human papilloma virus E6 and E7 gene-induced clonal expansion with intraepithelial proliferation of neoplastic transformed cells. The second latency period is between thick HSIL and invasive SCC.

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00515

CONSERVATIVE APPROACH IN THE MANAGEMENT OF YOUNG WOMEN WITH CIN2

22. Cervical neoplasia

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Background / Objectives

The better understanding of the natural history of cervical dysplasia is leading to the recommendation of more conservative approaches. Given the significant chance of
regression of CIN2 in young women and, on the other hand, the increased risk of negative obstetrical outcomes associated with its treatment, especially transformation zone excision (TZE), makes conservative approach an appealing approach.
Primary objective: Evaluation of the probability of CIN2 regression in untreated women under 30 years old.
Secondary objectives: Evaluation of the time until regression/progression and potential risk factors related to outcomes.

Results

Retrospective evaluation of the cases of women younger than 30 years old, with a diagnosis of CIN2 and who opted for conservative management (2012-2018). Follow up consisted of Pap smear, HPV test, colposcopy and biopsy according to colposcopy findings, every 6 months.
Regression was considered when there was no histological evidence of CIN2+ at 24 months. χ 2 test was used to evaluate categorical variables an t student for continuous ones; p values <0,05 were considered significant.

Conclusion

Out of 885 patients managed during this period, 15 were eligible for analysis.The mean age at diagnosis was 26.1±1.8 years old (22-29), 9 were smokers, and none was immunosuppressed.
Seven women were nulliparous at the time of diagnosis; 9 were combined oral contraceptive (COC) users; only one had history of previous HPV vaccination.
Regression was achieved in 5 cases; in 5 there was indication for TZE (CIN2

or CIN3); 5 are still in follow up. There were no cases of invasion.
In the 5 cases of regression, in 3 it occurred at 6 months, in one at 12 months, and another at 18 months. In three cases the genotype involved was the HPV16. HPV testing became negative in four cases (one at 6 months, two at 12 months and one at 24 months). Two of the cases in the regression group still have CIN1/LSIL.
There were 3 pregnancies in the group of women that had regression; one before and two after the regression.
Comparing the ones who had regression with the others, there were no differences concerning age at diagnosis, menarche, parity, use of COC, smoking, previous vaccination, referring Pap smear result, or HPV16 involvement.

References

Conservative management can be offered to compliant women, younger than 30 years, after a diagnosis of CIN2.
In this small sample it was possible to avoid TZE in almost half of the cases, with potential obstetric benefits.
The adoption of the LAST terminology may lead to a more aggressive and unnecessary approach in this population.

00001

NEW THERAPEUTIC REMOVAL APPROACH OF HEAVY FORMS OF CONDYLOMA WITH HIV, HEPATITIS AND IMMUNO COMPROMISED PATIENTS, WITH ADDITIONAL PROTECTION FROM PROFESSIONAL HAZARD TO THE DOCTOR PENDING PROCEDURE

30. Sexually transmitted diseases and HIV infection

I. Jeremic

Ordination Jeremic (Serbia)

Background / Objectives

HPV is the epidemic of the modern age, influenced to great extent by easy transmission of the infection.

With imuno compromised patients, and also those undegoing immuno suppresive therapy, (Corticosteroids and chemo therapy), incubation period is decreased to 3 weeks to three months.

It presents a therapuetic challenge due to the following:

1. Sensitivity of genitoanal region to forced trauma
2. Inaccesibility of the area, intraanal –vaginal and cervical condyloma
3. High vascularazitaion of vagina, cervix and hemorrhoids
4. Suceptibility of infection, bacterial flora (vagina and colon).
5. Weak immunity
6. Professional hazard

Results

The study included 100 patients of both gender 16 to 50 years of age, HIV and HbsAg positive, patients under immune suppressive chemo therapy, with medium

and heavy forms of condyloma on all parts of genitoanal region, with emphasis on cervix, vagina, anal and intraanal localization.

New technique of work employs two special types of radio access vaporization.1.Radio wave vaporization which involves the evaporation of cells infected with HPV virus, and Radio wave melting of the Condyloma masses is the second type of evaporation, it is used to moderate the medium and heavy forms of genital wart infections.

Conclusion

Therapeutic results of the new method are:

1. Almost bloodless operating field

2. Total precision and control in removing of all forms of genital warts in one act

3. Lateral damage to healthy tissue is less than 10 microns-

4. The recurrence rate is less than 3%

5. All interventions are performed in local anesthesia-duration up to 10 min

6.The therapy of choice for the pregnant women and immune deficient people

7.The working technique that protects doctors from the occupational exposure from HIV and positive Hepatitis B and C patient

References

With conditions of general immunodeficiency, with HPV infection in progress, the employment of new radio wave technique of condyloma removal ensured the principal precondition of successful therapy which consists of preservation of local immunity in the treated genitoanal region.

Since these patients have a problem with boosting of the immunity in general , new technique provides us with a solution and treatment of HPV infection in one go without complications such as infection, bleeding, pains, and heavy relapse.

References

In 2010- I was appointed Licensed Educator of radio wave surgery for Europe - Turkey and Russia in the field of gynecology and dermatosurgery by an expert team of doctors in New York.

I joined this team in 2012

Patented a special technique of radio access LOOP excision in young girls who have not given birth with severe precarcinoma on the cervix (CIN II, III) without narrowing and shortening of the cervical canal

4. Patented a special radio wave technique removing heavy form of Condyloma in both sexes at vagina mucosa, labia, anal and intraanal involving special bloodless of melting Condyloma mass with lateral damage to healthy tissue below 10 microns

Case studies are also presented at Medical Faculties in the USA as examples of treatment of first choice

The founder and the owner of "Polyclinic Jeremić" the Educational Center of radio wave surgery for Europe

FC 20. Low income countries

00071

HIGH PREVALENCE OF HUMAN PAPILLOMAVIRUS, HIV AND OTHER STI AMONG MEN WHO HAVE SEX WITH MEN IN TOGO IN 2017

02. Epidemiology and natural history

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Background / Objectives

No data are available on HPV prevalence in Togo. The aim of this study was to assess HPV, HIV and other STIs prevalence in Togo among the key population of men who have sex with men (MSM).

Results

A cross-sectional study was conducted in 2017 among MSM recruited in 4 cities of Togo (Lomé, Kpamilé, Atakpané and Tsévié) through the respondent driven sampling method. Participants' socio-demographic characteristics and sexual behaviors were recorded using a standardized questionnaire. Anal swabs were collected and sent to France to test HPV (Anyplex II^{TM}HPV28 Detection test detecting 19 high risk (hrHPV) and 9 low risk (lrHPV) HPV) and 7 STIs (Allplex^{TM}STI Essential Assay). HSV-1/2 were detected using RealStar®alphaHerpesvirus PCR Kit. HIV, Syphilis and HBs Ag screening were performed in Togo with SD Bioline HIV/Syphilis Duo® and Alere Determine^{TM}HBsAg tests.

Conclusion

207 MSM with a median age of 22 years (IQR=20-25) were enrolled. Prevalence of each STI is shown in the table.

	HIV	any type HPV	hrHPV	*N.gonorrhoeae* (NG)	*C.trachomatis* (CT)	*M.genitalium* (MG)	HSV-2	HBV	Syphilis
Prevalence (n=207)	26.1%	52.7%	44.9%	11.6%	9.7%	15.0%	8.7%	3.4%	0%

The any type and hrHPV prevalence were significantly higher among HIV-positive MSM compared with HIV-negative MSM (any type HPV: 88.9% vs 31.9%, $p<10^{-5}$; hrHPV: 85.2% vs 30.7%, $p<10^{-5}$). Other STIs, except HBV, were also more prevalent among HIV-positive MSM group (NG, p=0.03; MG, p=0.04; HSV-2, p=0.001 and a trend for CT, p=0.06). Having at least one hrHPV type detected in the anal canal was significantly associated ($p<10^{-5}$ for all) with the detection of other STIs, except HBV. Prevalence of each STI was significantly higher in MSM from Lomé than those recruited in other cities, excepted for HBV and HSV-2 (HIV, p=0.002; hrHPV, $p=2.10^{-5}$; NG, p=0.01; MG, p=0.04; CT, p=0.005). Most common hrHPV types were HPV35 (15.0%), HPV16 (13.0%), HPV31 (12.6%) and HPV59 (11.1%). Most common lrHPV were HPV6 (25.6%), HPV42 (17.9%), HPV40 (7.3%) and HPV11 (5.3%). HIV-positive MSM were more likely to have multiple any type HPV infections than HIV-negative MSM (85.2% vs 28.7%, $p<10^{-5}$). In multivariate analysis, HIV infection (aOR: 10.1, 95%CI: 4.0-25.6), HSV-2 anal excretion (aOR: 26.7, 95%CI: 2.9-244.3), CT anal infection (aOR: 11.7, 95%CI: 2.3-58.9), MG anal infection (aOR: 9.6, 95% CI: 3.1-29.9) and living in Lomé (aOR: 2.8, 95%CI: 1.1-7.1) were associated with increased risk of anal hrHPV infection. All participants with anal NG infection (n=24) were infected with at least one hrHPV.

References

These first data on HPV in Togo report high prevalence among MSM, highlighting the critical need of implementation of a national strategy regarding vaccination against Papillomavirus. We also described an unusual distribution of HPV types, with HPV35 being the most prevalent hrHPV.

00072

CERVICAL AND ANAL HUMAN PAPILLOMAVIRUS, HIV AND OTHER STI PREVALENCE AMONG FEMALE SEX WORKERS IN TOGO IN 2017

02. Epidemiology and natural history

V.M. Ferré [1], F.A. Gbeasor-Komlanvi [2], G. Collin [1], A.C. Dagnra [3], Q. Le Hingrat [1], M. Salou [4], D. Descamps [1], C. Charpentier [1], D.K. Ekouevi [5]

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Background / Objectives

In West Africa, limited data are available on HPV prevalence and on concomitant anal and cervical HPV infections. The aim of this study was to assess the prevalence of HPV, HIV and other STIs among female sex workers (FSW) in Togo.

Results

A cross-sectional study was conducted in 2017 among FSW recruited in hot spots (bars, clubs, streets, brothels) in 4 cities (Lomé, Kpamilé, Atakpané and Tsévié) following the respondent driven sampling method. Cervical and anal swabs were collected and sent to France to test HPV (Anyplex II^{TM}HPV28 Detection detecting 19 high risk [hrHPV] and 9 low risk HPV [lrHPV]) and 7 STIs (Allplex^{TM}STI Essential Assay). HIV and Syphilis antibodies screening were performed in Togo with SD Bioline HIV/Syphilis Duo^{TM}.

Conclusion

310 FSW with a median age of 25 years (IQR=21-32) were enrolled. Median ages of first sexual intercourse and of sex work initiation were 17 years (IQR=15-23) and 19 years (IQR=17-23), respectively. Prevalence of each STI is presented in the table.

	HIV	HPV any type	hrHPV	*N.gonorrhoeae* (NG)	*C.trachomatis* (CT)	*M.genitalium* (MG)	*T.vaginalis* (TV)	Syphilis
Prevalence (n=310)	10.6 %	45.2 %	39.7%	4.2%	6.1%	5.5%	6.5%	0.6%

Any type HPV prevalence was significantly higher among HIV-positive than HIV-negative FSW (63.6% vs 43.0%, p=0.03). Prevalence of other STIs were significantly higher in hrHPV-positive FSW for NG (p=0.004), MG (p=0.01) and showed a trend for TV (p=0.06) and CT (p=0.1). Prevalence of hrHPV, MG and TV were higher in FSW enrolled in Lomé than in other cities (p=0.02, p=0.04 and p=0.004 respectively). The most prevalent hrHPV types were HPV53 (6.5%), HPV58 (6.1%), HPV35 (5.8%), HPV31 (5.5%) and HPV16 (4.8%). The most prevalent lrHPV was HPV42 (6.5%). HPV6 and HPV11 prevalence were 3.2% and 0.6% respectively. Multiple hrHPV infections were more frequent in HIV-positive than in HIV-negative FSW (30.3% vs 14.8%; p=0.04). Both anal and cervical swabs were collected for 276 FSW. Prevalence of hrHPV was significantly higher in cervical than in anal swabs (40.2% vs 27.9%, p=0.003). hrHPV anal infections were significantly more frequent in HIV-positive than HIV-negative FSW (63.0% vs 24.1%, p<0.001). Prevalence of cervical hrHPV decreased with FSW's age while it was relatively stable for anal hrHPV prevalence. Concomitant anal and cervical hrHPV infections were present in 37% of hrHPV positive FSW but concordance was low (kappa coefficient=0.3).

References

These data report an unusual distribution of hrHPV types, with HPV16 only at the fifth rank. This study also reports one of the first analysis of both cervical and anal samples showing a high rate of concomitant HPV infections with low concordance. These findings highlight the critical need of implementation of a national strategy regarding vaccination against HPV in the female population.

00161

PREVALENCE OF HUMAN PAPILLOMAVIRUS AND OTHER SEXUAL TRANSMITTED INFECTION IN WOMEN FROM LAKE TURKANA AREA, KENYA

02. Epidemiology and natural history

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Background / Objectives

Invasive cervical cancer (ICC) is the most common women malignancy in Kenya. Scarce information is available about the high risk-HPV genotypes attributed to cervical cancer and sexual transmitted infections in the Lake Turkana area.

The objective of the study was to assess the prevalence and distribution of HPV types, Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis in cervical smears from women in north of Kenya

Results

A total of 161 women aged 13–75 years, visiting the Lodwar District Hospital, Kenia without gynecological medical purpose, were invited to participate in the study. All participants completed a detailed questionnaire and underwent a physical examination. Cervical specimens were tested for hr-HPV detection and genotyping by Multiplex Fluorescent-PCR F-HPV typing (Molgentix) and STI Allplex (Seegen) test for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG) and Trichomonas vaginalis (TV).

Conclusion

The overall HPV DNA prevalence was 31.2%. The most frequent type was HPV58 detected in 38% of positive cases (95% CI: 25.4–51.9), followed by HPV52 detected

in 12% (95% CI: 9.1–30.4), HPV16 and HPV-35 detected in 12% (95% CI: 5–23.3), HPV18 detected in 8% (95% CI: 2.5–18.1) and HPV33 detected in 8% (95% CI: 2.5–18.1).

The overall prevalence for STIs (CT, NG and TV) was 4.3% (95% CI: 4.1–11.2), 3.12% (95% CI: 3.8–8.8) for CT and 1.25% (95% CI: 3.8–8.8) for TV. NG was not detected. Among hr-HPV positive women, 6% (95% CI: 13.1–26.3) had STIs, while among HPV negative women was 3.6% (95% CI: 3.3–11.7). Six women declared to be HIV positive.

References

The high STIs prevalence observed in this population, suggests the need for health interventions to reduce the risk of infections.

00491

HPV VIRAL TEST IN PRIMARY SCREENING OF UTERUS CERVICAL CANCER AT THE NABIL CHOUCAIR HEALTH CENTER IN SENEGALESE WOMEN BETWEEN 30 AND 65 YEARS OLD.

09. HPV screening

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Background / Objectives

To describe the socio-demographic aspects of clients who have been screened for cervical cancer by an HPV viral test; Specify the diagnostic, therapeutic and follow-up aspects of the clients who had a positive test.

Results

This was a prospective, descriptive and analytical study conducted at the Nabil Choucair health center and at Ouakam Military Hospital from 01 May 2017 to 30 January 2018.

The study involved 144 patients who had received an HPV ABBOOT m2000 viral test.

The parameters studied included sociodemographic characteristics, clinical aspects, test results, diagnostic and therapeutic aspects, and follow-up.

The data was collected on a form and the statistical analysis was carried out by Epi-info 7.

Conclusion

We collected 144 women. The mean age of the patients was 39.9 years with extremes of 30 to 55 years. Patients were predominantly married (84%) and housewives predominated (48.1%) and slightly more than half (55.6%) were in school. More than half of the patients 61.8% were on contraception. Almost all patients (92.4%) were in genital activity. The average gestational age was 3.4 with and an average parity of 2.7. In our series, 103 patients (50.7%) had a history of abortions. The average age at marriage was 22.6 years and monogamous households predominated (56.8%). The average age at first intercourse was 22.1 years. The average age at first pregnancy was 23.9 years. More than ¾ of women (78.3%) had a partner; however, note that 21.7% of patients had 2 or more partners. The viral test was positive in 17 patients (11.8%). Papillomaviruses 16 and 18 were the most recovered. Colposcopy was normal and satisfactory in 9 patients (53%), 2 patients had atypical transformation of grade and 2 cases grade 2 (11.7%) 3 (17.6%) patients had viral colitis. Cervical biopsy was performed in 2 (11.7%) patients and histology showed CIN3 and microinvasive carcinoma. Therapeutic 02 conizations were performed. The postoperative course was simple.

References

The HPV viral test in primary screening for cervical cancer offers opportunities and is possible in developing countries such as Senegal despite limited means.

Keywords: HPV viral test, Nabil Choucair Health Center, Cervical cancer screening

00380

RESULTS OF A CERVICAL CANCER SCREENING PILOT STUDY IN MOROCCO COMPARING HPV ONCOPROTEIN E6 EXPRESSION TESTING AND VIA.

13. Screening methods

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Background / Objectives

MorocOncoE6 is a pilot study by the “Centre Mohammed VI pour le Traitement des Cancers”, Casablanca, Morocco and the “Clinic for Gynecology and Gynecological Oncology”, Charité-Universitätsmedizin Berlin, Germany, with support by the Ministry of Health, and Lalla Salma Foundation, Morocco. The primary objective of this study was to test feasibility of OncoE6™ Cervical Test (“OncoE6”; Arbor Vita, Fremont, CA, USA), including patient´s acceptance, compliance, and quality of the test results in comparison to visual inspection with acetic acid (VIA).

Results

This prospective cross-sectional study recruited women from 8 health posts (4 rural, 4 urban) in the Tangier area. All subjects were tested by OncoE6 and by VIA; for OncoE6, a physician and a self collected specimen were obtained from all subjects. All participants underwent colposcopy, and if indicated a biopsy and histology in a local pathology laboratory. The acceptability of sample self-collection was assessed via a semi-structured questionnaire to evaluate knowledge on cervical cancer, socio-demographic characteristics, medical history, and acceptability of the Evalyn brush-based self-collection. All study data were pseudonymized prior to analysis. The data

of the clinical results were given to the patients and follow-up visits and treatment have been established.

Conclusion

216 women of from rural (100) or urban (116) settings have been recruited. 15.5% (n=31) women had a positive/suspicious result on VIA, and 2.3% women tested positive on OncoE6 (self-collected or physician-collected). Multiplex HPV genotyping done at the Charite-Universitätsmedizin (Berlin, Germany) revealed high-risk HPV+ at 11.8% (n=21), with HPV16+ at 5.7% (n=12); other HR-HPV types detected were 51 (n=2), 66 (n=3), 68 (n=1), 73 (=1), 82 (n=1) with three subjects showing multiple infections. 3.1%, were diagnosed at CIN1, while no cases of CIN2 or worse have been observed. 82% of women provided a self-collected specimen, and 68% felt self-collection was straight forward. A control cohort of 20 patients with histologically confirmed invasive cervical cancers recruited at the Cancer Center in Casablanca also underwent OncoE6 testing.

References

This pilot study demonstrated a high degree of acceptability among the participating Moroccan women for cervical cancer screening and for self-sampling. VIA resulted in a substantial number of false positive test outcomes, which could cause costly overtreatment. The existing infrastructure in the target areas may allow for wider implementation of the OncoE6™ Cervical Test. A validation study in a multicenter and multiregional setting is planned.

00517

LOW-COST DIAGNOSTIC FOR THE IDENTIFICATION AND TYPING OF HUMAN PAPILLOMAVIRUS TO SUPPORT CERVICAL CANCER SCREENING IN LOW-RESOURCE SETTINGS

19. New technologies

C. Ortega [1], A. Steadman [1], S. Nelis [2], M. Selby [2], R. Gallagher [1], R. Rivera [1], N. Gachuhi [1], N. Wentzensen [3], M. Schiffman [3], J. O' Halloran [2], D. Bell [1], D. Madan [1]

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Background / Objectives

Human papillomavirus (HPV) infection is responsible for nearly all cervical cancer cases. The lengthy progression from infection to cancer makes screening highly effective in reducing cervical cancer cases and related deaths. Cytology-based screening programs have significantly reduced the burden of cervical cancer in developed regions. However, cytology-based screening must be performed frequently and is poorly suited to low-resource settings, where the vast majority of cervical cancer cases and deaths occur. Molecular HPV diagnostics are gaining usage but they are expensive and use is generally limited to centralized laboratories. For screening programs to achieve the same level of success in low-resource settings, an assay with high sensitivity and predictive value over a long period is imperative. Global Good and QuantuMDx are developing a point-of-care molecular diagnostic for the detection and genotyping of thirteen individual high-risk HPV (HR-HPV) types.

Results

The cassette-based assay is fully integrated, enabling sample to results in under one hour. The cassette runs on a portable, low-cost, battery-operated device. A vaginal or cervical swab is collected from a patient, the swab is placed in liquid medium, and a portion of the sample is loaded onto the cassette. Sample processing, target amplification, and target detection via DNA microarray hybridization occur on cassette without further user interaction. The assay detects a cellular control and genotypes thirteen HR-HPV types if present, which allows for risk stratification.

Conclusion

To date, we have assessed assay performance using contrived and patient samples, including vaginal and cervical swabs from two cohorts. Limit of detection is at or below 100 copies per reaction for each HR-HPV type in patient samples, no cross-reactivity has been detected with low-risk HPV types or non-HPV DNA, and assay performance is comparable with vaginal and cervical samples. Preliminary patient data are concordant with clinically-approved reference methods.

References

We expect the simplicity, affordability, and risk stratification provided by this assay to enable same day diagnosis and management at point-of-care.

00118

Introduction and Evaluation of A Simplest and Fastest Cervical Cancer Screening Technology for Resources Limited Area

35. Low resource settings

Y. Wang, X. Chen, Y. Zhijie, W. Rong, Z. Yu

Atila BioSystems, Inc. (United States of America)

Background / Objectives

Early HPV screening and treatment of precancerous lesions is known to be highly effective in drop of cervical cancer death rate. However, HPV infection is still a global issue, especially in poor resources area, even though there are many HPV screening technologies available. The main reason is that sample treatment to extract DNA for HPV detection is very expensive, time consuming and complicated, not to mention complicated expensive equipment required for HPV detection that limits the HPV screening globally. In contrast, AmpFire HPV technology has the simplest sample process (Atila BioSystems, an isothermal amplification to detect all 15 high risk HPV in a single tube reaction and simultaneously genotype HPV 16 and HPV 18, plus an internal control). It doesn't require extracting DNA, simply heats to lyse the samples and then it is ready for detection. In addition, amplification is extremely fast (40 minutes). AmpFire HPV can be finished within an hour from sample to answer (10 minutes heating). The simplicity and speed of AmpFire HPV assay will be a great fit for poor resources area for global HPV screening.

Objective: to evaluate the agreement of HPV detection between AmpFire HPV test and HC2 and their performance for HPV screening.

Results

Methods: A total of 80 patients samples were studied (samples collected in ThinPrep solution by Lehay Clinic, Burlington, MA). The AmpFire assay detects HPV virus by centrifuging 1ml ThinPrep sample solution, discharging the supernantant and then, the cell pellets were heat treated in a Atila lyse buffer for 10 minutes without DNA extraction. 2ul lysed simple was mixed with reaction solution for real time fluorescent detection in an hour. HC2 detection was done by Lehay Clinic following manufacturer's instruction.

Conclusion

Results: Comparing HPV results of Ampfire HPV to HC2, amount the 80 samples, 78 samples are agreed with each other (56 positive samples and 22 negative samples). One sample AmpFire is positive, but HC2 is called negative with cutoff value at 0.62 that is larger than other reported positive cutoff value at 0.2. The other disagreement sample detected by AmpFire as negative, but HC2 report as positive without reporting cutoff value from Lehay Clinic. The %OA (overall agreement) is 97.5%. %PA (positive agreement) was 98.2, %NA (negative agreement) 95.5%.

References

Conclusions: The Ampfire HPV assay performed equally well as HC2. Ampfire HPV assay did not require DNA extraction with very simple sample process and yielded results rapidly within an hour.

00234

PREVALENCE AND RISK FACTORS OF HPV AND OTHER SEXUALLY TRANSMITTED INFECTIONS AMONG 2000 WOMEN IN RURAL GHANA – FINAL RESULTS FROM THE ACCESSING* STUDY

35. Low resource settings

A. Krings [1], P. Dunyo [2], B. Hansen [2], C.M. Wormenor [2], I. Gedzah [2], E. Tekpor [2], S. Tetteh [2], A. Pesic [1], A.L. Behnke [1], D. Höfler [3], J.E. Amuah [4], G. Akwada [2], L.S. Manu [2], D. Holzinger [3], M. Pawlita [3], A.M. Kaufmann [1]

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Background / Objectives

Determine the prevalence and risk factors of 28 mucosal HPV and 18 other sexually transmitted infections among 18-65 year old women living in the North Tongu District, Ghana.

Results

This population-based study included 2000 women, representatively selected by geographical distribution, consenting to self-collect vaginal samples (Evalyn brush) and answer a questionnaire. Extracted DNA was HPV genotyped and presence of STIs determined by multiplex PCR and Luminex bead-based hybridization. Stata was used for regression analysis.

Conclusion

Median age of participants was 32 yrs (range 18-65 yrs). Majority of women had completed Junior High School, worked as traders/farmers, earned less than ~18€ per month, were married and had a median of 2 children. 1943 valid DNA samples were analyzed for HPV and 1937 for STI. High-risk HPV prevalence was 32.3% (95% CI: 30.2-34.5%), 9.7% (95% CI: 8.4-11.1%) of the women had multiple high-risk infections. The 5 most prevalent HPV types in descending order were 16, 52, 35, 59,

and 56. Risk factors by multivariate analysis were young age, not being married, and higher number of sexual partners.

Prevalence of *Chlamydia trachomatis* (CT) was 4.8% (95% CI: 3.9-5.9%), 2.5% (95% CI: 1.8-3.3%) for *Neisseria gonorrhoeae* (NG), and 4.1% (95% CI: 3.3-5.1) for *Trichomonas vaginalis* (TV). *Treponema pallidum* (TP) was detected in one sample only. NG and TV were associated with high-risk HPV infection.

References

Prevalence of high-risk HPV infections are higher than expected from the WHO/ICO HPV Information Centre estimates for West Africa (17.9%). Possible reason is an overrepresentation of women up to 34 years of age, who also happen to have the highest prevalence, compared to the general population in the district. Risk factors identified, such as young age, not being married, and higher number of sexual partners could be confirmed in this study. Condom use could not be assessed, as majority uses non-barrier methods (30%) or no (66%) contraceptive. Prevalence reported for WHO African Region for NG with 2.3% is similar, on the contrary WHO reported a CT prevalence of 2.6%, which is lower than our results. TP with only one case is far below the WHO reported seroprevalence of 3.5%. Differences may also reflect the fact that our sample is not representative of WHO African Region.

The high HPV prevalence highlights the need to increase efforts to vaccinate and screen women, as many are at risk of developing cervical cancer. STI and HPV prevalence seen are representative for the North Tongu District, Ghana and may vary from reported data for Western Africa. Given this context these results can guide future public health policy.

FC 21. Economics & modeling

00266

COST-EFFECTIVENESS OF PRIMARY HPV SCREENING WITH OR WITHOUT DUAL STAIN CYTOLOGY FOR CERVICAL CANCER

32. Economics and modelling

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Background / Objectives

Primary HPV testing could increase the detection rates of cervical intraepithelial neoplasia grade 2+ compared to cytology and it has been recommended as a cervical cancer screening option. The overtreatment due to the high sensitivity of HPV test still has the problem. The concept of dual stain has been introduced to decreased overtreatment case. The objective of this study is to identify the optimal cost-effective strategy for cervical cancer screening program by comparing the different algorithms which based on the use of primary HPV assay.

Results

We use a Microsoft Excel-based spreadsheet to calculate the number of accumulated cases of cervical intraepithelial neoplasia (CIN), invasive cervical cancer (ICC) and the budget impact of each screening program. The model was developed to determine the cost-effective of three screening strategies; pooled HPV test alone, HPV genotyping with reflex dual stain and pooled HPV test with dual stain. All strategies were considered a 5-year interval. Clinical parameters were combined data from the literature to estimate the performance of screening tests and natural history parameters. We assessed direct medical cost including screening and treatment cost. The main outcomes were the total cost, incremental quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

Conclusion

Strategy entailing HPV genotyping with reflex dual stain is the least costly strategy (total cost $37,893,407) and provides the similar QALY gained compared with pooled HPV alone with reflex dual stain (Average QALY 24.03). The two strategies which using reflex dual stain could increase screening performance and lower the prevalence of cervical cancer than pooled HPV alone. Pooled HPV test with reflex dual stain is more costly compared with pooled HPV test alone without reflex dual

stain. The incremental cost-effective ratio (ICER) was $10.09 per QALY gained. One way sensitivity analysis showed that the model is sensitive to the cost of dual stain and the cost of cancer treatment.

References

Decreasing the incidence of cervical cancer case and increasing the QALYs can be successful using dual stain cytology as the triage test for pooled HPV test or HPV genotyping. The result of our analysis favors the use of HPV genotyping with reflex dual stain as it offers the most QALY at the lowest cost.

00314

COST-EFFECTIVENESS EVALUATION OF HPV SELF-SAMPLING OFFERED TO NON-ATTENDEES IN CERVICAL CANCER SCREENING IN SWITZERLAND

32. Economics and modelling

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Background / Objectives

About 30% of women who are eligible for cervical cancer (CC) screening remain un-screened or under-screened in Switzerland. Human Papillomavirus (HPV) testing on self-collected vaginal samples (Self-HPV) for CC screening has shown to be more sensitive than cytology-based screening and to reach non-attendees. The objective of this study was to explore the cost-effectiveness of a Self-HPV-based screening in Switzerland.

Results

A recursive decision-tree with one-year cycles was used to model the life-long natural HPV history. Markov cohort simulations were used to assess the expected outcomes from the model. Three strategies were compared with the absence of screening: Self-HPV and triage with Pap cytology (Self-HPV/PAP), Self-HPV and triage with colposcopy (Self-HPV/colpo), conventional cytological screening and triage with HPV (PAP/HPV). Sensitivity analyses for the key parameters of the model were conducted to check the robustness of findings. Analyses were performed from the direct health care cost perspective, regulated by the Swiss tariff system.

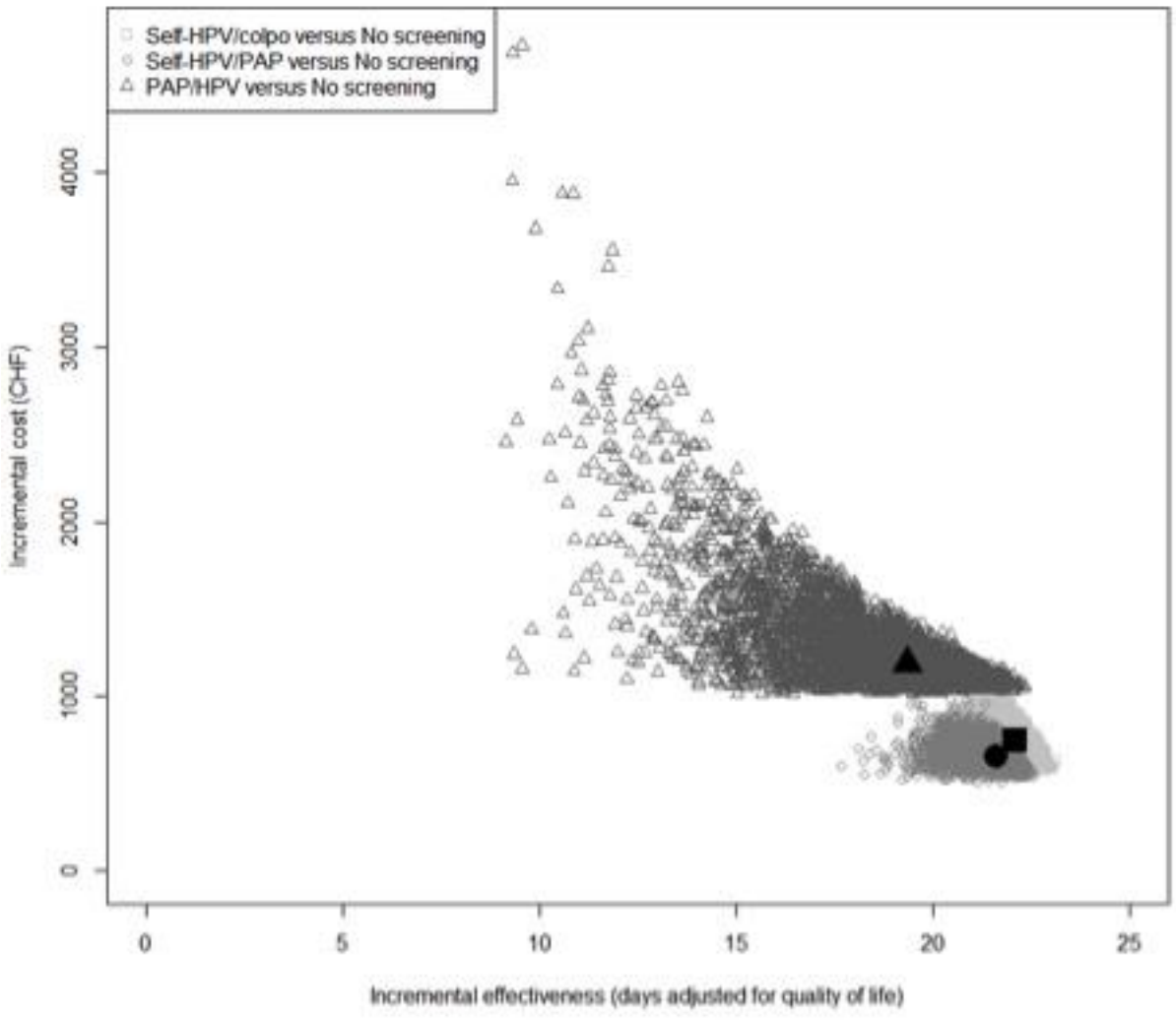
Conclusion

Compared with the absence of screening, offering a Self-HPV screening could prevent over lifetime 86 to 90% of CC and 90 to 91% CC-related deaths. Comparing to the currently cytology-based program, Self-HPV could reduce by 22 to 28% the lifetime CC cases and by 28 to 35% the number of CC-related deaths. Incremental

cost-effectiveness ratios (ICER) were estimated to be 11999 CHF per saved per Quality Adjusted Life Year (QALY) for the strategy Self-HPV/colpo, 10675 CHF per saved QALY for the strategy Self-HPV/Pap and 21108 CHF per saved QALY for the strategy PAP/HPV. Sensitivity analyses demonstrated that the ICER was robust to all parameters.

References

Offering Self-HPV as a CC screening strategy to non-attendees in Switzerland is cost-effective and is associated with a higher reduction of CC cases and related deaths compared to the currently used cytology-based screening.



00432

HEALTH IMPACT OF THE NINE-VALENT HPV VACCINE IN THE NETHERLANDS

32. Economics and modelling

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Background / Objectives

In 2009 the Netherlands have implemented HPV-vaccination in the Dutch National immunisation program (NIP) to prevent cervical cancer as around 700 women are still diagnosed with cervical cancer every year. The 2-valent HPV vaccine is currently used in the NIP. In 2015 the EMA licensed a second generation HPV-vaccine, the 9-valent HPV vaccine (Gardasil 9®) that protects against infections of seven high-risk HPV-types (HPV 16/18/31/33/45/52/58) and two low-risk HPV-types (HPV 6 and 11). This vaccine can prevent around 90% of all HPV-positive cancers, including cervical, vaginal, vulvar, penile, anal and head/neck cancers, and genital warts and around 82% of high-grade precancerous lesions. The aim of this study is to assess the health impact of the nine-valent HPV vaccine on HPV-related cancers, precancerous lesions and genital warts in the Netherlands.

Results

A previously published dynamic transmission model was calibrated on Dutch demographical and epidemiological data to simulate the HPV transmission dynamics and the occurrence of HPV-related diseases in the Netherlands. With the calibrated model predictions of the impact of HPV-vaccination are made over a period of 100 years comparing the status quo of offering the bivalent vaccine to 12 year old girls with a nine-valent vaccine for girls only and for boys and girls. In the two scenarios HPV-vaccine coverage of 53% and a two dose schedule were used to reflect the current HPV-vaccination program.

Conclusion

Replacing the 2-valent HPV vaccine with the 9-valent HPV-vaccine can, compared to the 2-valent vaccine, lead to an additional reduction of the incidence of CIN2/3 with 24.9% and cervical cancer (CC) with 12.5%, preventing 36996 CIN2/3 cases, 5564 CCs and 1409 CC deaths in 100 years. Girl only vaccination can also avert an extra 125 anal cancers (AC) and 20 anal cancer deaths (men and women combined). Protection against HPV-6/11 by the 9-valent vaccine can avoid 1.2 million of genital warts cases.

Extending the Dutch NIP with HPV-vaccination for boys will reduce the number of HPV-related cancers even further. Compared to the current program the 9-valent vaccine can prevent 7869, 5689, 1707, 976, 30 and 21 cervical, head/ neck, anal, penile, vulvar and vaginal cancers, respectively. The reduction of the HPV-related cancers can save almost 4000 deaths in 100 years.

References

The 9-valent HPV-vaccine can have a significant impact on the incidence of HPV-related disease compared to the 2-valent vaccine. Extending the HPV-vaccination program to boys will not only protect the vaccinated, but herd-effects will contribute to a better protection of the opposite sex as well.

00490

A SIMPLIFIED MODEL OF THE COST-EFFECTIVENESS OF SCREENING IN THE R PROGRAMMING LANGUAGE: A TEACHING AND RESEARCH TOOL

32. Economics and modelling

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Background / Objectives

To demonstrate a simplified pedagogical model of the cost-effectiveness of cancer screening and explain its potential as a teaching and research tool. Secondly, to show the model's relevance in the context of cervical cancer screening.

Results

The models applied in cost-effectiveness analyses of screening interventions are typically designed to address specific policy questions and consequently are often large, complex and opaque. We describe the rationale for employing a lightweight, fully shareable and transparent alternative to such applied models for the purposes of teaching and methods research. We present the code of a simplified, discrete-event, microsimulation model of cancer screening coded in the R statistical programme and supported with a Microsoft Excel-based user interface for the specification of input parameters. We demonstrate the components of the model relating to the natural history of disease, test performance and anticipated health gain and healthcare costs.

Conclusion

We show how the costs and effects of multiple alternative screening strategies can be simulated in the model. Using the process of comparative statics, we show how the efficient frontier and incremental cost-effectiveness ratios of alternative screening programmes vary with changes in key parameters such as disease incidence and test sensitivity. Furthermore, we demonstrate how the choice of the optimal screening policy for a given cost-effectiveness threshold varies with changes in input parameters. As such, the model provides a tool with which to demonstrate the qualitative relationships between parameters and the optimal policy in a way that is faster and more accessible than employing a full applied model. The relevance of this

model is demonstrated in the cervical screening context of varying risk groups between vaccinated and unvaccinated women and the choice between cytology and HPV-based testing.

References

The simplified model provides a transparent and easy-to-use demonstration of the fundamentals of the cost-effectiveness of screening. The model is fully shareable and represents a useful open-source teaching and research tool to enhance methods research in the cost-effectiveness of screening. Most models used in applied research are not fully published, due both to their large size and to concerns about sharing intellectual property. Such incomplete reporting compromises transparency and hinders methods research. Our simplified model avoids these problems with fully-shareable code that can be employed and adapted by anybody. This alternative offers a more appropriate tool for teaching the basics of screening cost-effectiveness and conducting methods research.

FC 22. HPV testing + genotyping

00122

Prevalence and genotype distribution of Non HPV-HR types in women with High grade cervical lesions in Northern area in Israel

09. HPV screening

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Background / Objectives

Invasive cervical cancer is caused by human papillomavirus (HPV). This study describes the prevalence and genotype distribution of low risk (LR) HPV types in women with high grade cervical lesions and cervical cancer.

Results

The study summarized HPV types detected in 6654 samples which were sent to the Serology laboratory from cervical clinics in northern Israel during the years 2006-2017. Four hundred and one women were diagnosed with CIN 2-3, and 205 with cervical cancer. The HPV test was performed during investigation of ASCUS (Atypical Squamous Cells of Undetermined Significance) results on Pap test or due to complaints suggestive of cervical neoplasia. Twelve HPV types were classified as high risk (HPV-HR) and the other Non HPV–HR types 40,42,53,54,56,62,67,70,73,81,82. (Non HPV-HR).

Conclusion

HPV-LR types were detected in 7.3% (28/379), and 4.8% (9/189) of women with Cervical Intraepithelial Neoplasia (CIN) 2-3, and women with cancer respectively. HPV was negative in 5.4 % (22/401) and 7.8 % (16/205) of women with CIN 2-3 and cervical cancer and respectively.

References

More data should be collected in order to decide if HPV screening should include more HPV types in order to improve detection rate of CIN 2-3 and cervical cancer.

Detection of Non HR-HPV types will be more important in the future after HPV vaccine which will decrease the prevalence of HPV 16 and 18.

00092

Identifying the causal HPV genotypes in high-grade cervical lesions using HPV genotyping of cervical screening samples

11. Genotyping

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Background / Objectives

To assess the clinical impact of HPV vaccination, the causal HPV genotypes in CIN2+ must be identified. The hierarchical and proportional methods are widely used for this purpose, but these ignore the occurrence of multiple lesions and do not adjust for the genotype distribution in the general population. We aim to develop a new method for identifying the causal HPV genotypes in CIN2+ based on cervical screening samples.

Results

Our model assumes that women may have multiple lesions caused by different HPV genotypes and that HPV genotypes have independent CIN2+progression risks. We applied our method to 512 women with abnormal cytology who tested positive for at least one of the 25 HPV genotypes detected by SPF10-LiPA. We validated our method by means of laser-capture microscopy (LCM)-polymerase chain reaction (PCR).

Conclusion

We predicted 274 type-specific lesion where 280 type-specific lesions, in 252 women, were observed by LCM. HPV16 and HPV33 had the highest estimated CIN2+ progression risk: 68% (95%CI: 61 – 75%) and 64% (46 – 83%), respectively. All low-risk HPV genotypes had negligible risk (i.e., <1%) of CIN2+. The genotype attributable fractions (AFs) estimated by our method were closer to the AFs observed by LCM-PCR than those estimated by the proportional and hierarchical methods. HPV16 and HPV31 were estimated to attribute the most: 0.47 and 0.15, respectively.

References

Our new method estimates HPV genotype attribution in cervical lesions accurately without prior assumptions about type-specific oncogenicity. This method can play an important role in monitoring HPV vaccine effectiveness.

00239

THE ROLE OF HPV GENOTYPING IN POST-TREATMENT FOLLOW-UP OF CERVICAL INTRAEPITHELIAL NEOPLASIA.

11. Genotyping

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Background / Objectives

Recurrences of cervical intraepithelial neoplasia (CIN) may occur in approximately 5-15% of cases within 2 years after conservative surgical treatment. Although many patient-related factors (age, smoking, number of sexual partners) and pathological characteristics of CIN (histological grade, glandular involvement and surgical margins) may affect the risk of recurrence, persistent positivity of HPV testing has been widely identified as the main predictor for the development of disease relapse. The aim of this study was to investigate the role of HPV genotyping for selecting women at high-risk of recurrence.

Results

Women undergoing surgical treatment of CIN, who performed HPV genotyping at baseline and the first follow-up visit, at the European Institute of Oncology, Milan, from January 2003 to December 2014, were selected for a retrospective analysis. HPV genotype was detected by the Roche Diagnostics Linear Array test on liquid-based cervical samples. HPV persistence was defined as the detection of at least one genotype at baseline that was still present after 6 ± 3 months. Relapse-free survival and the 2-years cumulative incidence were estimated by using the Cox and the Gray's models, covariates were infections status, baseline histology, age and HPV genotype.

Conclusion

Among 408 patients enrolled, HPV-persistence was shown in 89 women at the first follow-up. No significant difference was proven between HPV-not persistent and HPV persistent groups, according to age and baseline histology. Multiple infections were significantly associated to HPV-persistent patients (p=0.003). Overall, 26 relapses occurred, with a 2-years cumulative incidence of 10.6 (95% CI=6.7-15.6). HPV persistence (HR=6.2, 95% CI=2.7-13.8 and 2-years cumulative incidence of 26.1, 95% CI=14.1-39.7), multiple genotypes infection (HR=6.6, 95% CI=2.2-19.8 and 2-years cumulative incidence of 31.8, 95% CI=8.6-58.6) and the presence of HPV 16/18 with/without other high-risk genotypes (HR=8.3, 95% CI=3.6-18.8 and 2-years cumulative incidence of 31.3, 95% CI=16.7-47.1) were significantly associated to higher risk of relapse (p<.001). HPV 16 (60.0%) and HPV 18 (10%) were the most prevalent genotypes at follow-up, even if at baseline HPV 16 was the most frequent (33.0%) but followed by HPV 31 (26.3%) and HPV 58 (10.3%), whereas HPV 18 was not common (3.0%).

References

The detection of the same HPV-genotype at 6 months is a relevant predictor of recurrence. Moreover, persistence of HPV 16/18 has a significant impact on relapse-free survival. Therefore, HPV genotyping could be useful for a better risk stratification in post-treatment follow-up of CIN.

00242

SYSTEMATIC LITERATURE REVIEW ON TRIAGE STRATEGIES FOR HPV POSITIVE AND ASCUS/LSIL PATIENTS: ROLE OF EXTENDED HPV GENOTYPING VS OTHER TRIAGE METHODS

11. Genotyping

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Background / Objectives

Objectives: Advances in the screening and detection of cervical disease have been greatly aided by the inclusion of HPV testing along with cytology to identify patients at risk for CIN2+ disease. Various triage methods have been described in the literature to improve patient referral to colposcopy from HPV positive patients, as well as ASCUS and LSIL cases.

Results

Methods: We undertook a systematic review of literature to compare relative effectiveness of these triage methods. The analysis included PubMed, PubMed Central, the Database for Abstracts of Reviews of Effects, and the Cochran Database of Systematic Reviews from 2000 through 2017 for relevant controlled clinical trials and observational studies. In addition, a supplemental review was conducted by searching retrieved article references. Metrics of clinical effectiveness included incident detection of CIN2+ and colposcopy referral rates.

Conclusion

Results: 1281 articles were initially identified by the various search strategies. 255 articles were screened for inclusion/exclusion criteria and 45 articles were retrieved for data review and comparison. Finally, 20 articles were selected for data analysis and summary. Primary screening methods included cervical cytology and high risk HPV (hrHPV) testing. Triage methods evaluated in this systematic literature review included: (i) protein biomarker assays (e.g., immunocytochemistry with p16 and Ki-67; HPV E6 and E7 protein detection); (ii) HPV mRNA testing; (iii) DNA methylation markers; and (iv) HPV extended genotyping.

References

Conclusions: Relative to cytology-based triage of high-risk HPV positive patients, all the studied triage methods displayed varying degrees of utility in the detection of incident CIN2+ disease. HPV mRNA, protein biomarkers and HPV extended genotyping improved the detection of CIN2+ within ASCUS and LSIL cases. Protein biomarkers and DNA methylation represented an alternative to cytology in the triage of HPV positive patients. Protein biomarkers, DNA methylation and HPV extended genotyping displayed comparative negative predictive value over a 3-year follow-up period. In addition, the use of extended HPV genotyping permitted stratification of patients for immediate referral to colposcopy based upon increased risk for CIN2+ (HPV 16, 18, 31, 33) versus delayed colposcopy with re-testing at 1 year follow-up for certain HPV genotypes (e.g., 51, 56, 58, 59, 66). Protein biomarkers and extended HPV genotyping also reported reductions in colposcopy referrals. Additional comparative clinical studies appear warranted to directly compare these various triage methods within the same patient cohort for clinical utility and cost effectiveness.

00335

CLINICAL VALIDATION OF THE FULL GENOTYPING CLART4S HPV ASSAY ON SUREPATH COLLECTED SCREENING SAMPLES ACCORDING TO THE INTERNATIONAL GUIDELINES FOR HUMAN PAPILLOMAVIRUS TEST REQUIREMENTS FOR CERVICAL SCREENING

11. Genotyping

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Background / Objectives

“additional contribution”

Novel HPV assays intended for cervical screening use must be evaluated in accordance with International guidelines for Human Papilloma Virus test requirements for cervical cancer screening. The CLART HPV4S assay (CLART4S, Genomica, Madrid, Spain) is a PCR based microarray assay targeting the L1 region, and the first full-genotyping assay to detect oncogenic HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and three non-oncogenic-HPV genotypes (6, 11, 66) to achieve fulfillment of international validation criteria using SurePath screening samples. Here we present the outcome of the validation of this novel full-genotyping assay on SurePath collected screening samples, using the GP5+/6+ PCR assay (GP5/6) as a comparator/reference. The genotype concordance between CLART4S and GP5/6 was also assessed.

Results

To assess the performance of the CLART4S assay, SurePath screening samples from women 30 years and above participating in the Danish cervical cancer screening program were collected at Copenhagen University hospital, Hvidovre. For the clinical sensitivity analysis, 81 samples from women with confirmed CIN2 or greater were collected. For the clinical specificity analysis, 1184 samples from

women with less than CIN2 histology were collected. The assay results were compared to that of the GP5/6 assay in collaboration with Karolinska Institutet, Stockholm. The laboratory performance element involved testing 540 individual samples with known GP5/6 results. The inter-laboratory agreement was performed in collaboration with the Scottish HPV Reference Laboratory in Edinburgh, Scotland.

Conclusion

The relative sensitivity of CLART4S was 91.3% (GP5/6=92.6%) and relative specificity was 90.7% (GP5/6=91.0%). The CLART4S assay was shown to be non-inferior to that of GP5/6 for both sensitivity (p=0.00) and specificity (p=0.02). The genotype specific concordance between CLART4S and GP5/6 was good for 12 oncogenic HPV types. The Kappa value for intra-laboratory reproducibility was 0.84 (lower confidence bound 0.92) and for the inter-laboratory agreement the kappa value was 0.72 (lower confidence bound 0.87).

References

This is the first report on the clinical validation study of a full-genotyping HPV assay applied to SurePath collected samples. Using GP5/6 as comparator, the CLART4S performed well and met the International guidelines for sensitivity, specificity, intra-laboratory reproducibility and inter-laboratory agreement. The CLART HPV4S assay is therefore a good candidate for use in cervical cancer screening programs, especially programs utilizing genotype information in the screening algorithms.

00399

Comparison of partial HPV genotyping using the Cobas 4800 HPV test and the Aptima HPV 16 18/45 Genotype assay

11. Genotyping

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Background / Objectives

Partial HPV genotyping has the potential to further stratify HPV positive women in HPV primary screening. This study compares two partial HPV genotyping approaches, the Cobas 4800 HPV test for detection of HPV 16 and 18 and the Aptima HPV genotype assay for detection of HPV 16 and 18/45.

Results

In partnership with CervicalCheck, The National Cervical Screening programme, CERVIVA are undertaking a longitudinal observational HPV primary screening study which is evaluating different triage strategies for management of a HPV-positive primary screening test. Cervical cytology samples from approximately 13,000 women undergoing routine cervical screening will be tested for HPV DNA [cobas 4800 HPV test] and mRNA [Aptima HPV assay]. All HPV mRNA-positive women are further tested with the Aptima HPV 16 18/45 genotype assay for detection of HPV16 and 18/45. The performance of different genotyping strategies is being examined both cross-sectionally and longitudinally over two screening rounds for detection of CIN2+.

Conclusion

In total, 9853 primary screening samples were tested for HPV DNA and mRNA. Overall, 4.8% [469/9853] tested positive for HPV 16/18 DNA and 3.6% [357/9853] for HPV 16/18/45 mRNA. There was good agreement between both assays for detection of HPV 16/18 and HPV 16/18/45 (97.67%, Kappa co-efficient: 0.678). The HPV 16/18

DNA positivity rate was significantly higher than HPV 16/18/45 mRNA positivity rate in women who were normal on cytology [2.9% vs 1.7% p=<0.001]. There was no significant difference in the rate of positivity in women with LSIL/ASCUS [18.4% vs 17.5% p=0.643] and HSIL [62.9% vs 58.6% p=0.211] between the Cobas HPV test and the Aptima HPV 16 18/45 genotype assay respectively. The Linear Array HPV genotyping test (Roche) was used elucidate a subset of discordant samples.

References

Overall there was good agreement across both assays. The Aptima HPV 16 18/45 genotype assay had fewer positives in women who were normal on cytology. Longitudinal follow up data will determine and compare the clinical performance of each genotyping assay for detection of high grade cervical neoplasia.

00088

ASSESSMENT OF ATTRIBUTION ALGORITHMS FOR RESOLVING CIN3-RELATED HPV GENOTYPE PREVALENCE IN MIXED-GENOTYPE BIOPSY SPECIMENS USING LASER CAPTURE MICRODISSECTION AS THE REFERENCE STANDARD

19. New technologies

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Background / Objectives

Determining the single causative HPV genotype of each high-grade cervical lesion and/or cancer is an important measure of vaccine effectiveness in preventing vaccine-type-specific disease. Laser capture microdissection (LCM) and genotyping of lesions is considered the gold standard: however, it is resource-intensive and many large studies use easier-to-collect samples and mathematical algorithms to attribute genotype where multiple genotypes are detected. To date, these algorithms have not been assessed against LCM genotyping.

Results

Cervical biopsy specimens (n=531) containing cervical intraepithelial neoplasia grade 3 (CIN3) lesions were genotyped as whole tissue sections (WTS) (RHA kit HPV SPF10-LiPA25, v1.0 and SPF+ strips). LCM, and proportional, hierarchical, single type only and maximum (any type) attribution methods were used to resolve mixed genotype detections. LCM was also used to re-test any samples that were negative for high-risk-HPV genotypes.

Conclusion

Figure 1. Comparison of nonavalent HPV genotype prevalences generated by different methods to resolve mixed-genotype detections in CIN3 biopsy specimens.Of 531 specimens, 14 were excluded from analysis (13 invalid DNA results, 1 could not

be resolved to a single genotype using LCM), leaving 517. Of these, mixed-genotype detection occurred in 71 (13.7%) of WTS. The results of the 5 attribution methods are shown in Figure 1for nonavalent vaccine genotypes. There were no statistically significant differences between proportions of each genotype by attribution method, although proportional attribution provided the lowest genotype-specific prevalence estimates overall.

References

In CIN3 biopsy specimens, including mixed-genotype detections, attribution algorithms to resolve mixed infections to a single causative genotype gave comparable results to the reference method LCM.

FC 23. Molecular markers 2

00199

GROWTH POTENTIAL AND APOPTOSIS IS INHIBITED BY LOCALISED TOPICAL MICROWAVE ENERGY IN HPV16-POSITIVE CERVICAL TUMOUR CELLS IN 3D TISSUE CULTURE MODELS

01. Viral and molecular biology

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Background / Objectives

Raising the temperature of tissues into the “fever” range of 38-45°C as a therapeutic is known as hyperthermia. Localised hyperthermia has been used previously as an adjuvant to cancer therapies [1]. In the case of benign lesions, microwave treatment of HPV-positive verrucas resulted in 75.9% clearance of lesions [2]. We characterised the molecular effects of microwave treatment on in vitro cultured HPV-16 positive cervical cancer tissues as a potential new therapy for HPV-associated disease.

Results

The medical device, “Swift” (Emblation Ltd, UK) delivers microwaves through a 7mm contact site and is currently used in the clinic for the treatment of verrucas. The delivery of the microwaves to tissues results in heating to around 48^{o}C and causes apoptosis of nearby cells. SiHa cells containing the integrated HPV16 genome were grown on organotypic raft cultures and treated with the Swift device. Immunohistochemistry and immunofluorescence microscopy (antibodies against HPV E6, p53, cleaved caspase 3, Ki67, MCM2, HSP70, G3BP) was used to determine the molecular effects of the device. Quantitative PCR was used to measure expression of immune modulators.

Conclusion

Microwaving induced apoptosis at the treatment site alongside a reduction in cellular growth/proliferation. HSP70 expression was observed in regions of the rafts treated with the microwave device, confirming hyperthermia. The levels of the HPV E6 oncoprotein were downregulated by the treatment and levels of p53 were upregulated in a sustained manner in tissue areas adjacent to the treatment site.

Microwaving induced translational stress but did not induce conventional inflammatory pathways.

References

Current treatments for anogenital pre-cancers and warts are painful and invasive. We aimed to characterise the effects of microwaving on HPV-infected tissue as a potential less invasive method of eliminating disease. The delivery of microwaves via the Swift probe, allows the natural apoptosis of HPV-infected cells to resume. Therefore, the Swift probe presents as a promising new, less painful treatment for the elimination of HPV-infected cells in anogenital lesions.

References

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00237

K14-HPV16 MOUSE MODEL: A JOURNEY TOWARDS EARLY HPV-INDUCED HEAD AND NECK VS ANAL AND UTERINE CARCINOGENESIS

01. Viral and molecular biology

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Background / Objectives

Human Papillomavirus (HPV) is the most common sexual transmitted agent worldwide, being also responsible for 5 % of all human cancers. Even though cervical cancer is thought to be reducing, HPV positive anogenital and head and neck cancers are regrettably increasing. Differences in the natural history of HPV have been observed by gender and anatomic sites of infection where epithelial backgrounds and tissue microenvironment may play a crucial role. The main goal of this study was to understand if E6, E7 and E5 oncoproteins may promote distinct roles in the carcinogenesis cascade in K14-HPV16 mice model base of tongue, anus and uterine cervix characterized by different tissue microenvironments.

Results

The base of the tongue, anus and uterine cervix samples were collected from 10 female and 10 male 30-week-old K14-HPV16 transgenic mice. Histopathological analysis of the tissues was performed for tissue characterization. Tissue samples were classified as normal, hyperplasic, dysplastic and carcinoma. The E6, E7 and E5 mRNA levels were quantified by real-time PCR being normalized by a combination of the best two housekeeping genes. Statistical analysis was performed using the IBM SPSS Statistics (Version 24.0). Mann-Whitney tests were used to evaluate statistical differences in normalized relative expression (–ΔCt) of the E6, E7 and E5 genes among the different tissue samples.

Conclusion

We observed a higher incidence of more advanced lesions, namely dysplasia and carcinoma on the base of the tongue tissue samples in comparison with the uterus and anus where all lesions were hyperplasic. The expression of the oncogenic HPV viral mRNA was detected across tissues with no significant overexpression within the different lesions.

References

This study enlightens the proof of concept of an earlier and less-cofactor dependent carcinogenesis induced by HPV in oropharyngeal cancers in comparison with other anatomic localizations. In the base of the tongue, cancer was induced within the mice 30 weeks period, in comparison with the anus and uterine cervix, where HPV itself seems not to be sufficient to promote advanced lesions even though the expression of the viral mRNA´s are detected and similar within the tissues. Future studies should focus on understanding the behavior of the HPV oncoproteins and the related oncogenic pathways at multiple anatomic locations of infection, representing different tissue microenvironments. This might allow a better understanding of tissue-specific HPV-related carcinogenic steps and a consequent precision therapy.

00250

HUMAN PAPILLOMAVIRUS (HPV) DNA DETECTION IN PLASMA AND IN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) SAMPLES OF WOMEN WITH A RECENT HISTORY OF CERVICAL DYSPLASIA

01. Viral and molecular biology

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Background / Objectives

The presence of viral DNA has been suggested to represent a marker for viral associated cancers. Some studies have reported the presence of HPV DNA in the bloodstream of women with cervical cancer, indicating the possible circulation of HPV-associated cancer cells. On the contrary, the presence of HPV DNA in blood of women with precancerous lesions has been less frequently reported. The aim of this pilot study is to investigate the presence of HPV DNA in cervical, plasma and PBMCs samples of women with a recent history of cervical dysplasia.

Results

Paired blood and cervical samples have been collected from 53 women referred for colposcopy at San Gerardo Hospital, Monza, Italy. Nucleic acids extraction was performed using NucliSENS easyMAG (bioMérieux). HPV detection in cervical samples was assessed by real-time PCR using AnyplexII™ HPV28 (Seegene). HPV 16, 18, 31, 33, 45, 51 and 52 DNA detection on plasma and PBMCs was performed using highly sensitive quantitative "in house" genotype specific real-time PCR assays. Genotype-specific oncogenic transcripts detection was assessed by “in house” real-time RT-PCR assays using the iTaq™ Universal SYBR ® Green One-Step Kit.

Conclusion

One or more HPV types were detected in 83% (44/53) of cervical samples, with HPV16 and HPV31 resulting the most prevalent genotypes. Seven of the studied women (7/53; 13.2%) were found to be HPV DNA positive in plasma samples.

HPV16 resulted the most prevalent genotype in plasma, with an average viral load of 336 copies/ml. Of these, only one woman was shown to have the same genotype in both cervical and plasma samples. Preliminary results of HPV DNA detection in PBMCs have shown a positivity of 4%, 2/53 (HPV16 in both cases), with a viral load of 6.87E+01 copies/10^5 cells and 1.32E+01 copies/10^5 cells respectively. One of these two samples was also positive for the presence of HPV16 oncogenic transcripts.

References

These preliminary results confirm that HPV DNA can be detected in peripheral blood samples of women with a recent history of cervical dysplasia and that oncogenic transcripts can be identified in PBMCs. Further studies are required to evaluate the significance of the presence of high-risk HPV DNA and RNA in the bloodstream of women with early stages of cervical dysplasia.

00218

mRNA biomarker detection in liquid-based cytology: a new approach in the prevention of anal cancer

12. Molecular markers

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Background / Objectives

Anal cancer (AC) incidence has increased in certain populations such men who have sex with men (MSM), HIV-positive individuals and women with high-risk human papillomavirus (hrHPV) infection.

hrHPV is considered the main etiological agent of AC, leading premalignant lesions (high-grade intraepithelial lesion/anal intraepithelial neoplasia grade 2-3 [HSIL/AIN2-3]). Current literature suggests that screening for anal HSIL/AIN2-3 should be considered in high-risk groups using liquid-based cytology (LBC) and high-resolution anoscopy (HRA). However, the success of this strategy has not been proved. Other studies have shown that hrHPV testing and triaging with molecular markers might be an approach for AC screening.

We aimed to determine the feasibility of the detection mRNA expression of CDKN2A/p16, MKi67 and TOP2A in anal LBC to evaluate whether these biomarkers might be useful in the identification of patients with HSIL/AIN2-3.

Results

We included 125 MSM positive for HIV (MSM-HIV) referred to the AC unit of our center during 2016. At the initial visit, patients undergo anal LBC, hrHPV testing, HRA and at least one biopsy. We selected MSM-HIV with cyto-histological concordant results in the first visit. MSM-HIV included in the study were grouped into three categories: control group (men with a negative Pap test, biopsy and hrHPV testing; n= 77), low-grade SIL group (LSIL; patients with a Pap test and biopsy showing LSIL and positive hrHPV testing; n= 28), and HSIL group (men with Pap test and biopsy of HSIL and positive hrHPV testing; n= 20). After RNA extraction (RNeasy RNA extraction kit; Qiagen), the expression of CDKN2A/p16, MKI67 and TOP2A was analyzed by reverse transcription and quantitative PCR in LBC. The data were analyzed with SPSS Version 19.0.

Conclusion

Mean normalized ΔCycle threshold (ΔCt) of the different biomarkers for the control, LSIL and HSIL group did not differ significantly. For TOP2A, ΔCt (95% confidence interval [CI]) values were 64.8 (13.6-116.1); 44.4 (21.2-67.6) and 19.4 (9.8-29.1), respectively; p 0.587. For MKi67 ΔCt (95% CI) values were 101.0 (0.1-202.5); 42.9 (14.8-71.1) and 13.2(5.7-20.6), respectively; p= 0.535. For CDKN2A ΔCt (95% CI) values were 3.5 (2.4-4.6), 3.0 (1.7-4.2) and 1.0 (0.6-1.3), respectively, for the different diagnostic categories; p=0.062.

The area under the ROC Curve (95% CI) for CDKN2A/p16, MKI67 and TOP2A were 0.74 (0.66-0.82), 0.73 (0.64-0.80) and 0.60 (0.51-0.69), respectively.

References

mRNA detection in anal LBC specimens is feasible. Further studies including a larger number of patients are warranted to confirm that biomarker identification using mRNA-based strategies might have a role in the secondary prevention of AC.

00255

Identification of productive and transforming cervical and anal intraepithelial neoplasia using immunohistochemical markers p16INK4a and HPV E4

12. Molecular markers

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Background / Objectives

To improve diagnosis and identify lesions needing treatment, biomarkers that show distinct expression patterns between transforming and productive high-grade squamous intraepithelial lesions (HSIL) are needed. We investigated the expression of immunohistochemical biomarkers HPV E4, a marker of productive HPV infection, and $p16^{INK4a}$, a marker of transforming HPV infection, in cervical and anal intraepithelial neoplasia (CIN and AIN).

Results

A reference grading was established using expert, consensus, subjective HE diagnoses supported by p16 expression for 243 cervical and 183 anal biopsies. Worst lesions were scored for p16 (0-4), identifying transforming infections and HPV E4 (0-2), marking the productive aspect of the lesion.

Conclusion

Reference grading resulted in: 78 CIN0, 46 CIN1, 37 CIN2, 82 CIN3, 37 AIN0, 67 AIN1, 43 AIN2, 36 AIN3. In both CIN and AIN, proportion of diffuse p16 positive lesions increased with the severity of the lesion (100% of CIN2 and CIN3, 91% of AIN2 and 97% of AIN3). Significantly more AIN1 lesions showed extensive patchy p16 staining compared to CIN1 ($p<0.001$). HPV E4 was positive in very similar

proportions of CIN0 and AIN0 (0% and 0%), CIN1 and AIN1 (46% and 49%), CIN2 and AIN2 (49% and 56%) and CIN3 and AIN3 (6% and 3%).

References

Combined p16/E4 staining can provide detailed information beyond supporting H/E classification, that could potentially allow more selective treatment of HSIL. Differences in p16 expression between CIN and AIN might relate to differences in site, involvement of HIV and progression which need to be considered in managing screen-detected lesions.

EUROGIN 2018
Abstracts

PART III - POSTERS

00336

THE DEVELOPMENT OF A PRIMARY CELL MODEL FOR THE INVESTIGATION OF DOUBLE STRAND DNA REPAIR IN HPV-ASSOCIATED GYNAECOLOGICAL CANCERS

01. Viral and molecular biology

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Background / Objectives

The DNA damage Repair (DDR) pathway is crucial for maintaining chromosomal integrity following challenges by genotoxic insults and is potentially a key determinant of cellular sensitivity to multiple modalities with potential to treat squamous gynaecological cancers including chemotherapeutics, ionising radiation and PARP inhibition. HPV is acknowledged to manipulate the DDR pathway at multiple junctures to facilitate viral replication, and a greater understanding of the consequences of this on double strand DNA (dsDNA) repair in HPV positive tumours may enable an enhancement of therapeutic efficacy and the identification of biomarkers to indicate resistance to conventional treatment.

HPV positive tumours of the oropharynx and genital tract are generally considered more radiosensitive than HPV negative tumours. In vitro studies have demonstrated that in the presence of HPV E6 and E7, cells can exhibit delayed dsDNA repair kinetics, potentially due to the preferential recruitment of DDR proteins to sites of viral DNA (1,2). To our knowledge a comprehensive study of dsDNA repair kinetics in cells derived directly from HPV positive tumours has not been undertaken. We therefore set out to develop primary cells from cervical and vulvar cancers to use as a model for the study dsDNA repair following exposure to ionising radiation.

Results

Fresh tumour (and adjacent normal) tissue was collected intra-operatively from 14 patients undergoing surgical procedures for the management of squamous cancers of the cervix or vulva at Liverpool Women’s Hospital, UK. Following initial processing the tissue was incubated in selective media on Cellbind plates until explants formed. Explanted cells that were successfully passaged had DNA and RNA extracted for mycoplasma testing, HPV 16&18 E6 and E7 PCR and Short Tandem Repeat analysis to confirm origin from primary tumour sample. Cell pellets were subjected to

p16 staining and DNA/RNA ISH for high risk HPV. All cell lines demonstrated pan-cytokeratin staining.

Primary cells (passages 3 to 6) were then assessed for radiation sensitivity by clonogenic assay, and this data was correlated to the evaluation of DDR proteins including RAD51, ATM, H2AX and FANCD2 by immunofluorescence and Western blotting at serial timepoints post 2Gy of ionising radiation.

References

HPV positive and negative primary cells derived from gynaecological squamous cancers and adjacent normal tissue can be successfully developed and used as a comparative model to evaluate dsDNA repair in these tumours. This resource should allow further characterisation of the important relationship between HPV and the DDR pathway, which is desirable to refine the current treatment protocols for HPV positive cancers and look towards the development of new therapeutic strategies.

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00527

ANALYSIS OF HUMAN PAPILLOMAVIRUS AND DNA PLOIDY IN CERVICAL LESIONS

01. Viral and molecular biology

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Background / Objectives

Cervical cytology remains the main screening method for cervical cancer, although the detection of human papillomavirus (HPV) oncogenic types has been gaining ground in screening programs. In addition to these methods, aneuploidy identification is a marker of neoplastic transformation and it is associated with progression from precancerous lesions to invasive cancer. The objective of this study was to investigate the ploidy behavior and the presence of high-risk HPV types (hr-HPV) in precancerous cervical lesions.

Results

One hundred and two women were referred to colposcopic and biopsy examinations after an abnormal cytology result. Cytological samples were collected in ThinPrep® solution for molecular identification of HPV types by Microarray DNA after PCR amplification. Slides were stained by the Feulgen method for nuclear analysis. DNA ploidy analysis met the requirements established by the 4th European Society for Analytical Cellular Pathology (ESACP) Consensus in DNA image cytometry (DNA-ICM).

Conclusion

From 102 patients, 75.3% were positive for hr-HPV and 53.9% had an aneuploid profile. Among patients with aneuploid DNA, 92% were positive for hr-HPV types. According to histological result, 45% of cases without lesion were positive for hr-HPV and 15% were aneuploid. Among cases of cervical intraepithelial neoplasia (CIN) grade 1, 64% were positive for hr-HPV and 20% revealed aneuploidy. In CIN 2 cases, 79.9% were positive for both hr-HPV and aneuploid DNA. All CIN 3 patients were positive for hr-HPV, while 82.4% of CIN 3 patients were aneuploid. All cases of squamous cervical cancer (SCC) were DNA aneuploid, while 66.7% were positive for hr-HPV. No DNA was found in the sample diagnosed as adenocarcinoma in

situ (AIS), but this case was aneuploid. Both cases diagnosed as adenocarcinoma (AC) were positive for hr-HPV and proved to be aneuploid. High risk HPV types were present in 84.2% of CIN 2+ (CIN 2, CIN 3, AIS, AC or SCC) cases with a significant relationship. The relationship between aneuploidy and CIN 2+ cases was also significant, with aneuploidy being present in 82.5% of CIN 2+ cases. When both hr-HPV and aneuploidy were positive, they were present in 68.4% of CIN 2+ cases. HPV 16 was the most frequent HPV type observed, followed by types 31, 35, and 58.

References

DNA aneuploidy was increasingly observed in relation to the precancerous lesions severity progression, whereas oncogenic HPV types were observed in a more balanced manner. Thus, the use of hr-HPV identification along with a DNA ploidy profile could be useful to identify high-grade lesions and indicate which lesions have the greatest potential for progression.

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00622

HIGH THROUGHPUT MOLECULAR TESTING FOR HPV: PERFORMANCE OF THE ONCLARITYTM HPV ASSAY ON A NEW HIGH THROUGHPUT SYSTEM VERSUS THE VIPERTM LT SYSTEM

01. Viral and molecular biology

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Background / Objectives

The BD COR™ System is a new high throughput, automated and modular molecular platform designed to address the pre-analytical challenges of today's clinical laboratories. The BD COR™ System focuses on providing efficiency, competitive performance and flexibility by simplifying sample sorting complexities, reducing hands on time and the potential for manual errors, and providing scalability to satisfy a broad range of molecular testing needs. The system is intended to offer a portfolio of assays that provide diagnostic solutions in the areas of microbiology and women's health. The study described here compares performance of one assay, the BD Onclarity™ HPV Assay, tested on the BD COR™ System versus the BD Viper™ LT System using simulated specimens stored in BD SurePath™ Preservative Fluid and Hologic PreservCyt® Solution.

Results

Contrived panels were prepared by spiking BD SurePath™ and PreservCyt® media with quantified C-33A (background cervical epithelial cells), SiHa (HPV16), HeLa (HPV18) and MS751 (HPV45) cells to simulate cervical specimens comprising HPV infection at low target levels to challenge the system. Spike levels for each of the tested genotypes included Negative (C-33A only), High Negative (C5), Low Positive (C95) and Moderate Positive (3xC95) as determined using the BD Onclarity™ HPV Assay on the BD Viper™ LT System. For each media type, a total of 81 replicates were tested for each spike level of each genotype across 3 BD COR™ and 3 BD Viper™ LT systems. A two one-sided test method (TOST), using an α-level equal to 0.05, was used to assess equivalence across the two test systems. A pre-determined allowable margin for the difference in mean Ct.score values between BD COR™ and BD Viper™ LT systems was assigned to be ±0.75. Performance at each of Negative,

C5, C95 and 3xC95 levels for each of HPV16, HPV18 and HPV45 genotypes was assessed across 3 BD COR™ systems relative to the reference of 3 BD Viper™ LT systems.

References

Performance of the BD Onclarity™ HPV Assay using the BD COR™ high throughput molecular system when tested with contrived panels is equivalent to the same assay performed on the BD Viper™ LT System.

* The BD COR™ System is under development and is not available for sale or use.

00013

INCIDENCE OF CERVICAL LESIONS ASSOCIATED WITH HUMAN PAPILLOMAVIRUS INFECTION IN WOMEN LIVING IN TRIBUTARY COMMUNITIES OF AMAZONAS RIVER - BRAZIL

02. Epidemiology and natural history

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Background / Objectives

Introduction: Cervical cancer remains a word public health problem. The relationship between this neoplasia and human papillomavirus infection is well established. In Brazil, the National Cancer Institute (INCA) predicts that there will be 16,300 new cases of the disease in 2018. There are no reports of cases about this neoplasm in the riverine populations of the Amazon River and its tributaries, leaving this population deprived of medical assistance and programs of cancer prevention.

Objective: The present work aims, by using a liquid-based cervical cytology followed by a Human Papillomavirus (HPV) genotyping, to identify the incidence of HPV infection, a precursor lesion of cervical cancer, in cervical samples from women living in the riverside of Negro and MadeiraRiver.

Results

Method: 123 cervical samples were collected in a liquid medium (Cellpreserv) and automatically processed on KLP 2000 equipment (KolplastÔ). Two cytologists analyzed the cellular material subjected to conventional Papanicolaou staining and classified the results by Bethesda System (2011). The HPV genotyping was performed using the MicroArray (EuroimmunÔ) method in duplicate. Data were analyzed statistically by the Mann-Fisher exact test and the chi-square test. The study was duly approved by the Ethics Committee of the Santo Amaro University - SP (Brazil Platform - CAAE: 61414216.4.0000.0081).

Conclusion

Results: Of the 123 cellular samples, 65 samples were from Negro River riverside population and among of them 12.32% showed squamous intraepithelial lesions with

neoplastic potential such as ASCUS (1.54%), LSIL (6.15%) and HSIL (4.62%). The highest incidence of HPV types were 16, 45, and 61 (21.43%). Others 58 cellular samples were from Madeira's riverside population and 6.7% showed cervical intraepithelial lesions with neoplastic potential, of them ASCUS (1.72%), LSIL (1.72%) and HSIL (3.45%) The incidence of HPV infection, in both regions, was 31 (25.20% samples analyzed by molecular test, being HPV 16 (4,87%) and HPV 45 and 53 (3,25%) the most prevalent types. The highest incidence of HPV infection was in womenaged less than 25 years (43.75%) and over 50 years (27.27%), compared to women aged between 26 and 49 years (X2= 9.64 p = 0.0081). Viral infection was more frequently found among single women than married women (p = 0.0412).

References

Conclusion: Our results showed a high risk of developing cervical neoplasia in young and single women due to the great incidence of high-grade squamous intraepithelial lesions(HSIL) associated with HPV types of high oncogenic risk found in women living in the riverside communities near the Madeira and Negro River, tributaries of the Amazon River.

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00027

PHYLOGENETIC CHARACTERISATION OF HIGH RISK HUMAN PAPILLOMAVIRUS GENOTYPES ISOLATED FROM GAMBIAN WOMEN

02. Epidemiology and natural history

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Background / Objectives

High risk human papillomavirus and its variants are known to cause approximately 90% of cervical cancer, a leading cause of death amongst women globally. Oncogenicity varies according to the HPV genotype, as well as the lineage of some genotypes. HPV is markedly heterogeneous and more than 150 genotypes have been identified, which are classified into types, lineages, and sub-lineages based on analysis of the structural late gene protein (L1 gene).

Aim of study: To sequence and identify HPV isolates from reproductive aged women attending a sexual health clinic in Banjul, Gambia, and compare these with previously published sequences of isolates from other geographical locations.

Results

A 450 base pair region of L1 gene was amplified by PCR using PGMY 09/11 consensus primers. Amplified PCR products were purified and sequenced, and BLASTn searches of the generated sequences were carried out for initial HPV genotype identification. The Gambian sequences were then aligned with other representative sequences of HPV genotypes using MUSCLE and a Maximum Likelihood phylogeny was generated in MEGA7 under the conditions of the T92+G model with 1000 bootstrap replicates. The measure of divergence within and between genotype specific clades was also calculated using MEGA7

Conclusion

Six different high-risk, and two probable high-risk, HPV types were detected which were HPV58, HPV52, HPV16, HPV51, HPV56, HPV66, and HPV73 and HPV53, respectively, with the newly generated sequences sharing 90-100% nucleotide similarity with previously published sequences of these different HPV genotypes in GenBank. The most common genotype detected was HPV52. Phylogenetic analysis confirmed the identity of the Gambian samples of which each grouped within its respective HPV genotype clade. Within each genotype Gambian samples clustered with reference-sequences from different geographical regions but no distinct geographical lineages were identified. Overall only low levels of inter and intra divergence between the representative viral sequences were detected

References

Low levels of divergence between the Gambian L1 gene HPV genotype sequences and those from other geographical localities illustrate a probable rapid radiation event of these specific HPV genotypes. However, owing to the low levels of diversity between the sequences and the lack of geographically distinct lineages it was not possible to identify potential origins of HPV in Gambia. Current results could illustrate either a recent invasion event of these HPV genotypes into Gambia or, more likely, could be recent movement of HPV from Gambia mediated by the historical movement of people.

References

00033

IDENTIFYING BIAS CAUSED BY MULTI-TYPE HPV INFECTIONS IN TYPE-SPECIFIC PROGRESSION PARAMETER ESTIMATES

02. Epidemiology and natural history

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Background / Objectives

Type-specific progression and clearance parameters are typically estimated for each HPV type separately. However, such estimates may be influenced by multi-type infections. The parameters can also be estimated simultaneously for all HPV types by applying a multi-type model. Our aim with this study was to investigate the differences between single-type and multi-type estimation procedures for type-specific parameters and how different conditions influence these estimates.

Results

A simplified progression model was built for two (generic) HPV types with given type-specific progression and clearance parameters. The model was used to produce a simulated data set from which the type-specific parameters were estimated in two ways: 1) single-type estimates for both types separately, and 2) multi-type estimates for both types simultaneously. The single- and multi-type estimates were compared to the original parameters with which the data was produced. To investigate the conditions under which the estimates differ, the procedure was repeated with different progression and clearance parameters.

Conclusion

The multi-type estimation procedure provided reliable and accurate estimates of the progression and clearance parameters. Under the considered conditions single-type estimates included up to 40% bias. The error in single-type estimates was largest when there was a 50% difference between the two type-specific progression rates and smallest when the types were both progressing at an intermediate rate.

References

Single-type estimates for progression and clearance may be biased by multi-type HPV infections. Our results with two HPV types give motivation to extend the inference to a realistic multi-type model.

00042

DECIPHERING THE KINETICS AND ECOLOGY OF HUMAN PAPILLOMAVIRUS (HPV) GENITAL INFECTIONS IN YOUNG WOMEN

02. Epidemiology and natural history

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Background / Objectives

Human papillomaviruses (HPVs) are responsible for one third of infection-induced cancers [Total et al. 2011 Prev Med]. Most studies focus on chronic infections and cancers, and we know little about the early stages of the viral infection [Alizon et al. 2017 Viruses]. In particular, the roles in infection clearance or persistence of the immune system, the microbiota and the virus genetics remain poorly understood. We designed a longitudinal study to unravel the course of HPV genital infections in young women.

Results

This study combines mathematical modelling, bioinformatics and clinical research. We follow longitudinally 150 young women (aged 18 to 25) visiting an STI detection centre in Montpellier (France). HPV negative women visit every 4 months and HPV positive women visit every two months. All women are required to perform 8 self-samples at home between visits. At each visit, a gynaecological exam is carried out and samples are collected to measure HPV virus load, systemic anti-HPV antibodies induction, local cytokine levels, and determine HPV genotype and local immune cell response. These data consist in time series, which will be used to fit mathematical models. In addition, we sample genital microbiota using eSwabs to analyse its interaction with HPV infection.

Conclusion

Our preliminary data show that HPV prevalence is high in the study population but the longitudinal follow-ups are very consistent in terms of types. We are also able to analyse local immune cells using a ten color panel by flow cytometry and to detect specific cytokines.

References

This study will provide us with one of the most detailed natural history studies of acute HPV infections in young women and their interactions with the host immunity and the vaginal microbiota. It will also allow us to investigate related issues regarding HPV genetic diversity, vaginal microbiota dynamics and sexually transmitted infections in general.

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00070

SIGNIFICANT DISPARITY IN THE PREVALENCE OF LOW-RISK BUT NOT HIGH-RISK HPV GENOTYPES AMONG HIV POSITIVE MSMs AS COMPARED TO HEALTHY WOMEN

02. Epidemiology and natural history

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Background / Objectives

Although the anus and the cervix share some anatomical/histological similarities, in particular with respect to the presence of a susceptible transitional zone, it is previously shown that anal HPV infection tends to be more diverse and persistent than HPV infection of the cervix. This diversity tends to widen when one compares cervical HPV infections among healthy women with anal HPV infections among HIV positive MSMs.

In a country where a-free-of-charge HPV vaccine is provided in a gender-neutral manner, it is of interest to understand the details of which genotypes predominate in which anatomical site and among which population group. The aim of this epidemiological study is to assess disparities in the distribution of HPV genotypes among HIV positive MSMs and healthy screening women in Austria.

Results

Out of a total of 813 sexually active men (n= 271) and women (n=542), 355 HPV positive adults were selected for this analysis. Anal swab samples collected for STD screening among HIV positive MSMs and cervical swab samples collected as part of the routine cervical cancer screening program were additionally examined for 40 HPV genotypes using a reverse line blot hybridization method. Sociodemographic and behavioral data were collected using structured questionnaires.

Conclusion

Considering all 813 study participants the prevalence (95% CI) of overall HPV infection was 90% (86.3-93.4) among HIV+ MSMs and 20.5% (17.0-23.8) among healthy women. HPV positivity was significantly associated with age, age at sexual debut and number of life time sexual partners (LSP) in both study population, but smoking showed significant association only with cervical infection. Although HIV+ MSMs have higher prevalence of all detected genotypes as compared to cervical infections in women, a closer look into those HPV-positive study participants (n=355) revealed that MSMs have a statistically significant higher proportion of LR-HPV types whereas the HR-HPV genotypes predominate among women. Multivariable adjusted OR (95% CI) for the distribution of LR-HPV among this high risk population was 7.3 (2.25-23.5) whereas that of HR-HPV types was 0.19 (0.05-0.79).

References

Considering existing data (based on laser capture microdissection) which suggest that LR-HPV types might be occasionally associated with anal cancer, our finding of significant predominance of LR-HPV needs a closer scrutiny. The observed discrepancy in the distribution of HR- and LR-HPV among these two population groups suggests that factors other than the number of life time sexual partners (significantly higher in HIV+ MSMs) might play a role in the acquisition and pathogenesis of HPV.

00102

PREVALENCE OF HIGH-RISK HPV IN A REGION OF PORTUGAL: ANALYSIS OF DATA FROM PATIENTS REFERRED FROM CERVICAL CANCER SCREENING

02. Epidemiology and natural history

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Background / Objectives

In Portugal's North region, a population cervical cancer screening was implemented. Women were tested for high-risk HPV and referred to consultation if they tested positive for HPV16 or HPV18 or if they had other high-risk HPV (hr-HPV) associated with cytology abnormalities. The aim of this study was to characterise the population referred to the Inferior Genital Tract Unit of Centro Hospitalar Póvoa de Varzim/Vila do Conde, in particular the prevalence of different HPV serotypes.

Results

We conducted a retrospective study analysing the clinical cases of 138 women referred to consultation in our Unit after cervical cancer screening during an eighteen-month period (from January 2017 to June 2018). Clinical data – such as demographic data, motive of referral, HPV serotype(s) and colposcopy and biopsy results – was extracted and analysed. Results were compared to those of the Cervical Lesions Observed by Papillomavirus Types-A Research in Europe (CLEOPATRE).

Conclusion

The women were aged between 25 and 64 and none of them were immunised against the HPV virus. The main reason for referral was hr-HPV and atypical squamous cells of undetermined significance (ASC-US) in the cytology, followed by presence of HPV16 or 18, and in third place by hr-HPV and a cytology showing low-grade intraepithelial lesion (LSIL). The most prevalent serotype was HPV 16 (present in 20% of women), followed by HPV 31 (11%); HPV 18 was present in 8% of women;

hr-HPV other than these were present in 60% of the population studied. In particular, serotypes not covered by the nonavalent vaccine (HPV 68, 39, 66, 51, and 59) were found 71 times in the population studied (HPV 68 was in fact the third most common serotype). Infection by multiple serotypes affected 32% of women, being more frequent in the younger population.

References

In our (non-vaccinated) population, the most common serotypes are 16 and 31, which is in line with the results of the CLEOPATRE study. In contrast, the rate of multiple serotype infection was significantly higher than the one described in that study (32% vs 7%). In addition, the serotypes 68, 39, 66, 51, and 59 were quite common in our population. This finding raises questions about the potential negative impact in the disease evolution in the future, after nonavalent vaccination. Further studies and epidemiological monitoring is, therefore, necessary in our particular population.

00127

ANALYSIS OF HPV 18 DIVERSITY AMONG WOMEN WITH DIFFERENT MORPHOLOGY DIAGNOSIS IN RUSSIAN FEDERATION

02. Epidemiology and natural history

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Background / Objectives

Cervical cancer takes first place in morbidity of women of reproductive age in Russian Federation. HPV 18 is detected in about 14% of invasive cervical cancer. Despite numerous investigations in the world there is still lack information about HPV 18 diversity in Russian population.

Results

This part of work is preliminary to whole genome sequencing of about 1000 samples of HPV 18 type from RF with different morphology diagnosis. To evaluate distribution of HPV 18 variants, URR and E6/7 genes from 35 samples were sequences by Sanger method. 22 samples have histology confirmed CIN2+diagnosis, 11 – negative for intraepithelial lesion and malignancy.

Conclusion

All samples belong to A variant, among them one sequence obtained from patients with carcinoma in situ diagnosis clustered together with A1 lineage reference sequence, and one from patient with LSIL – together with A4 variant reference sequence. Most of other sequences were close to A3 lineage. There was neither correlation with histology/cytology diagnosis nor with viral integrated/nonintegrated form.
Interestingly, two samples from patients with NILM cytology diagnosis formed separate branch with 0.7% dissimilarities from closest variant A4. Both samples have integrated viral form.

References

Molecular epidemiology of HPV is a blank space in Russian Federation despite high rate of cervical cancer mortality and morbidity. We obtain preliminary data on distribution of HPV18 lineage on territory of Russian Federation. HPV 18 population is quite uniform and belong to A lineage, as it was shown for HPV 16. Yet we cannot elicit any influence of HPV 18 variant on morphology diagnosis due to small amount of samples.

00136

A CLINICAL AUDIT ON HPV PREVALENCE AMONGST CERVICAL LESIONS IN MALTA

02. Epidemiology and natural history

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Background / Objectives

Human Papillomavirus (HPV) infection has been established as the main causative agent of cervical lesions worldwide. HPV may rest in a latent phase up to the trigger of a transformation event, where lesions are induced; these varying from LSILs to HSILs which may eventually progress to SCC. Different HPV sub-types may cause different lesion severities. The aims of this retrospective clinical audit are mainly to assess the prevalence of HPV-induced lesions together with the most prevalent hr-HPV subtypes in Malta and to correlate the HPV genotypes to histology and cytology results.

Results

The study by Falzon et al. (2013) analysed all CIN3 and invasive carcinomas over the period 2000-2013 in Malta, using a Multiplex HPV genotyping assay and RT-PCR techniques on FFPE tissue. HPV Prevalence Data was obtained through the study carried out by Zahra et al. (2018) which included the different hr-HPV sub-types in Malta over 3 years (2015-2018). 96 HSIL LLETZ Histology cases, excised from 2011-2017 were extracted from Mater Dei Hospital Laboratory records. COGNOS® Software was used to extract the data required. All LBC Specimens, with a suspected lesion from April 2018 up to June 2018 were assessed for the respective result of HPV genotyping.

Conclusion

The study by Falzon et al., (2013) indicated that between the period 2000-2013, 91% of invasive cervical carcinomas were found to be HPV positive, with HPV 16 being the most prevalent genotype. HPV 16, followed by HPV 56 were also the most prevalent genotypes in the study carried out by Zahra et. Al (2018). Results obtained through the Mater Dei Hospital Histopathology laboratories demonstrated that the LLETZ specimens diagnosed as HSIL from the period 2011-2017 were most prevalent in the age group 31-35 (35.4%), followed by the 26-30 age group (22.9%). 16.7% of HSIL LLETZ cases were diagnosed in the 36-40 age group whilst 12.5% and 11.5% of cases fell in the >40 and the 20-25 age groups respectively. One case was reported to have had a HSIL LLETZ excision under 20 years of age.

References

This study has shown that in concordance with worldwide studies, HPV16 is the most prevalent HPV subtype in Malta, causing the majority of invasive cervical carcinomas, however HPV56 is the second most prevalent HPV subtype. The fact that certain high-risk cytologically abnormal cases had a negative HPV result indicates the possible presence of additional hr-HPV subtypes. This study has provided information about the distribution of HPV genotypes in Malta, as well as the HPV genotypes mostly associated with high-grade cervical lesions. It is also part of an ongoing study involving the use of molecular biomarkers for prediction of HPV transformation events, possibly leading to optimised techniques for improved patient diagnoses.

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00206

A Cohort Study on the cervical precancerous lesion demographic character, prevalence and Practice onits association with Human Papillomavirus Virus subtypes between Iranian populations

02. Epidemiology and natural history

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Background / Objectives

Retrospective study has reported that cervical cancer is the most common gynecologic malignancy around the world. At the first sight, based on the long-time interval between the pre-cancerous phase and this malignantprogression,and the simple available screening test,in the other hand the well-known correlation between cervical lesion (mainly squamous cell subtype) andhuman papillomavirus, its prevention seems to be simply achieved. Despite all of this concept near 270000 woman's death per year is due to this malignancy.

This study aimed to assess the demographic data on Human papillomavirus infected patient and the reliability of the present screening test, and to establish any correlation between the sub type of human papilloma virus(HPV) and cervical lesion progression among Iranian woman in Mashhad.

Results

This cohort study was conducted on 562 patients with cervical intraepithelial neoplasiaand cancer,who was referred to the Gynecology Clinic at Ghaem Hospital-Iran- Mashhad from Nov2016 to Feb 2018. All patients demographic, familial, nutritional, clinical feature, previous screening (consist of Pap smear and HPV typing test) and diagnostic test (colposcopic biopsy samples) results were collected and analysis by SPSS.

Conclusion

Among 562 patients who included in the study, cervical intraepithelial lesion grade 1, 2&3 and cancer cases were 430, 100 and 32 patient, respectively.The mean age was 36+/-9 years in pre-cancerous lesion group versus 47.2+/-8 years in malignant cases.No significant difference was identified between cervical lesionand weight, smoking, alcohol drinking and parity. (p >0.05). In analysis of the contraceptive method usage between patients with cervical lesion there were found many cases of cervical intraepithelial lesion who had used barrier (condom) even and unfortunately most of the patient had no method of contraception at all.Present screening Guideline in Iran is based on the adequacy of Pap test among women over 30 years old, meanwhile, there is no need for screening, HPV infection among women, so far not in younger age; but in this study, the mean age of first sexual intercourse was 19 years old and even under the age of thirty there were detected multiple cases of cervical pre-cancerous lesion.

References

An organized cervical cancer screening is a necessity for Iran as more than 500-900 women in middle age diagnosed with an invasive cervical cancer every year cannot be ignored. This recommendation should be taken into account by the National Health System of Iran and Muslim countries with shared culture and behavior patterns. Cobas HPV test could be consideration in countries Muslim country with appropriate budget, resources and facility.

00295

Prevalence of Human Papillomavirus among adolescents after introduction of school-based HPV vaccination in Norway

02. Epidemiology and natural history

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Background / Objectives

The objective of the study is to assess the effect of school-based HPV-vaccination by comparing type-specific HPV prevalence between vaccinated and non-vaccinated women of the first cohort offered vaccination in Norway.

Results

Facebook advertisement was used to recruit women born in 1997, the first cohort to be offered school-based HPV vaccination. Self-samples were collected from the vagina, using Evalyn Brush®, Rovers. All samples were HPV-typed using modified general primers (MGP)-PCR followed by hybridization of type-specific oligonucleotide probes (Luminex technology), detecting and genotyping 37 HPV types. Sexual habits were ascertained through a short questionnaire. Self-reported vaccination status was validated via linkage to the Norwegian Immunization Registry (SYSVAK). Multivariate Poisson regression was used to calculate prevalence ratios (PR). All presented PRs are adjusted for lifetime number of sexual partners, age at sexual debut and time since last intercourse.

Conclusion

Of 562 women who completed the registration form, 315 returned a self-sampling device and were included in the study. Among the 312 women with complete data, 239 (76.6%) had been vaccinated with at least one dose of quadrivalent HPV (qHPV) vaccine prior to sexual debut. Prevalence of any HPV type was similar for both vaccinated (38.5%) and unvaccinated (41.1%) women (PR: 0.97, 95% CI: 0.63-1.48). Prevalence of at least one high risk HPV type was 19.2% in both vaccinated and unvaccinated women (PR: 1.07, 95% CI: 0.58-1.99). Prevalence of qHPV types was

low in the cohort overall at 1.9%. Prevalence of qHPV vaccine types was 0.4% for the vaccinated women and 6.8% for the unvaccinated (PR: 0.04, 95% CI: 0.00-0.42).

References

Among the first cohort of women receiving school-based HPV-vaccination in Norway, overall prevalence of any HPV was similar for vaccinated and unvaccinated women. We observed lower prevalence of qHPV vaccine types among those who received at least one dose of qHPV vaccine before sexual debut, after adjusting for sexual behavior. However, this result was based on small numbers and should therefore be interpreted cautiously.

00388

Human papillomavirus (HPV) cytology and genotype distribution in vaccinated women from East-Flanders, Belgium

02. Epidemiology and natural history

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Background / Objectives

The human papillomavirus (HPV) vaccination program for young women has been introduced in Flanders (Belgium) since 2010. Monitoring of changes in the prevalence of HPV infection has been proposed as a useful tool to detect breakthrough infections and possible shifting in genotype distributions. However, data on HPV prevalence under vaccination are limited. The objective of this study was to evaluate the prevalence of HPV infection and genotype distributions among vaccinated women attending a public hospital.

Results

Women presenting at the gynecological department of AZ Jan Palfijn hospital in Ghent were recruited during 110 consecutive days. Cervical smear samples were collected to perform cervicovaginal cytology. The Cobas® HPV Test was performedto identify HPV types 16 and 18 while concurrently detecting other high-risk (HR) types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) without individual identification. Vaccination information was collected using standardized questionnaires.

Conclusion

Out of 2979 specimens, information about the vaccination status was available in only 114 (3.8%) cases. Ninety-five (83%) patients were non-vaccinated (23-63 year). In the group of 19 (17%) vaccinated women (21-46 year), one patient was vaccinated with Cervarix®, seven with Gardasil®, one with Gardasil 9®and for three patients vaccine type could not be specified. In the vaccinated group, three specimens were classified as NILM (one HR HPV+), three as LSIL (all HR HPV+), eleven as ASC-US (eight HR HPV+), one as ASC-H (HR HPV+) and one as HSIL (HR HPV+). All detected HPV types were identified as other-high risk types expect one ASC-US specimen that showed positivity for HPV16 and other high-risk types.

References

There is a need for a longitudinal monitoring program to determinepostvaccinal changes in genotype distributions and breakthrough infections. Since the intepretation of our findings is hampered by the lack of sufficient vaccination data, future research should include an optimized strategy in retrospective data collection (e.g. consultation of the national vaccination register) and full genotyping.

00454

BREAST CANCER ASSOCIATED TO HPV AND CONCOMITANT PARTNER WITH A HISTORY OF PENILE CANCER

02. Epidemiology and natural history

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Background / Objectives

In the last twenty years, many papers have described the relation between breast cancer and Human Papillomavirus (HPV). Recently, we have published an article relating the presence of HPV identified by multiplex nested Polymerase Chain Reaction (PCR) tests in the tumor tissue in 50 of 100 breast cancer diagnoses in the Federal University of Ceará (UFC) Hospital. After this publication we started a research which was approved by the Ethics Committee No 2.396.348-2017 of UFC, in order to identify how HPV approached the ductal system in the breasts of the patients examined at the Grupo de Educação e Estudos Oncológicos (GEEON). The objective of this case report is to present a case of a woman with breast cancer that had a partner with a history of penile cancer.

Results

After January 2016, all patients in GEEON breast service have been investigated for HPV diagnosis history in previous cervical cancer screenings followed by dermoscopy of the nipple and biopsy of suspected HPV-contaminated areas, oral and vaginal swab examinations, Immunohistochemistry tests for P16 in the breast tumor biopsies and PCR testing of the tumor sample and punch biopsy of the nipple in order to confirm HPV. A 37-year-old patient named MLS with a 3cm diameter malignant tumor in her upper right quadrant of the right breast, when asked about HPV, did not know if she had genital HPV, but knew that her husband had penile cancer associated to HPV diagnosed 3 years prior. We took a core biopsy of the tumor and a dermoscopy-guided punch biopsy of an area of the nipple tissue with abnormally high vascularization to identify traces of HPV in the tumor and the nipple. In addition, the patient underwent oral and vaginal swab tests to identify traces of HPV.

Conclusion

HPV 16 and 33 were identified oral cavity of the patient with breast cancer. In the paraffin-shaped biopsy of the breast tumor and of nipple, were identified HPV 6 and 11. The p16ink4a was positive in breast cancer sample. But cervical and vaginal samples were negative for HPV. The HPV 6 and 11 were also identified in the penile specimen of her partner and p16ink4a was expressed too.

References

Presence of HPV at various genital and non-genital sites of an illustrative case of breast cancer patient and partner with penis cancer opens up prospects for further studies that may elucidate the actual natural history of the virus especially with regard to breast cancer. Nipple tissue and Breast Cancer positives to same genotypes of penile cancer of sexual partner could suggest that the virus could reach the ductal system of her breast through sexual intercourse.

00466

CERVICAL ADENOCARCINOMAS, HUMAN PAPILLOMAVIRUS TYPES AND ASSOCIATION WITH AGE; AN ASSOCIATION STUDY

02. Epidemiology and natural history

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Background / Objectives

Background/Objectives: Cervical cancer is the second most common type of cancer in women. Infection by high-oncogenic risk human papillomaviruses (HPV) is the principal causal factor of the development of cervical cancer. HPV 16 and 18 predominate in squamous cell carcinomas and adenocarcinomas, followed by HPV 45. The objective of this study was to evaluate the specific HPV types present in women diagnosed with cervical cancer and identify associations with age and histological type.

Results

The hematoxylin-eosin stained slides were reviewed and the cases were then selected according to the histological diagnosis obtained. The paraffin blocks corresponding to those slides were separated to perform further testing using molecular techniques. A total of 106 paraffin-embedded tissue blocks from biopsies performed in cervical cancer patients, 84 cases of squamous cell carcinoma and 22 cases of adenocarcinoma, were selected. HPV detection and genotyping were performed using the INNO-LiPA HPV Genotyping assay (Innogenetics)

Conclusion

The age of the patients at cervical cancer diagnosis ranged from 26 to 91 years, with a mean of 52.3 years (95% confidence interval (95%CI: 49.3 - 54.7). The mean age of the patients with a diagnosis of adenocarcinoma was 46 years (95%CI: 40.7 - 51.3) compared to 53.9 years (95%CI: 49.7 - 56.2) for the women with a diagnosis of squamous cell carcinoma. Women diagnosed with adenocarcinoma were significantly younger than those diagnosed with a squamous cell carcinoma (p=0.04). In 56.6% of these cases, HPV 16 was found as a single infection and in 14.3% in combination with other HPV types as a multiple infection. HPV 18 was found in 12 cases: in 7.5% as a single infection and in combination with HPV 16 in 3.8%. Positivity for HPV 16 in single infection or in combination with other HPV genotypes was significantly associated with a diagnosis of squamous cell carcinoma while adenocarcinomas were associated with HPV 18 in single or multiple infections. A significant association was found between age <50 years at the time of cervical cancer diagnosis and a histological diagnosis of adenocarcinoma (OR = 4.31; 95%CI: 1.45 - 12.80; p = 0.007). Women <50 years of age with cervical cancer were 5.41 times more likely to test positive for HPV 18 when compared to those infected with HPV 16.

References

The variation in the prevalence of HPV types according to age may be the result of a progression of precursory lesions of cervical adenocarcinoma containing HPV 18 considering that this type is often integrated into the host genome.

00558

HIGH RISK HUMAN PAPILLOMAVIRUS IN A GROUP OF PORTUGUESE WOMEN

02. Epidemiology and natural history

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Background / Objectives

Human Papillomavirus (HPV) is the etiological agent for cervical cancer and genital warts. Worldwide, cervical cancer is the fourth most common cancer in women and the high risk HPV (HR-HPV), namely HPV 16 and 18 are responsible for the most of the cases. The objective was to analyze the HR-HPV frequency in a group of women referred for HR-HPV testing.

Results

Clinical samples from 3117 women were perform by Cobas® HPV test (Roche Molecular Systems, CA, USA), this assay detected HPV 16 and HPV 18 and 'Other HR-HPV' (-31,-33,-35,-39,-45,-51,-52,-56,-58,-59,-66 and 68). Positive samples for 'Other HR-HPV' were sequenced for genotyping using MY09/11 primer´s.

Conclusion

HR-HPV frequency was 20.8% (649/3117). Among the positive samples, 'Other HR-HPV' was the most common (72.8%; 473/649). HPV 16 and 18 were detected only in 22.8% (148/649) and 7.4% (48/649) of the cases, respectively. 7.4% (48/649) of the positive women were infected with more than one HPV (34 with 'Other HR-HPV' + HPV 16; 8 with 'Other HR-HPV' + HPV 18; 5 with 'Other HR-HPV' + HPV 16 + HPV 18 and 1 with HPV 16 + HPV 18). Sequencing of 'Other HR-HPV' is ongoing and preliminary results shown the majority frequency for HPV 31 (11.7%) followed by HPV 56 (9.1%) and 8.9% for the HPV 66.

References

The HR-HPV frequency is high (20.8%), 30.4 % of these women were infected with HPV 16 or HPV 18 which is a high frequency. This study reveals the importance of the implementation of screening programs, and the use of HPV detection.

00607

Human Papillomavirus infection in gynecological cancers in Latvia: From the epidemiological data to clinical impact

02. Epidemiology and natural history

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Background / Objectives

According to the United Nations (UN) definition, the Baltic countries belong to the group of countries whose economy is in transition. This transition period has created changes in life-style, priorities, and living standards. On a global scale, the New Independent States (NIS) of the former Soviet Union have an intermediate incidence of cervical cancer, the main etiologic factor of which is Human Papillomavirus (HPV), a major sexually transmitted disease (STD). Recently, the prevalence of all STD has exploded in these countries. In parallel with the increase of STD and because of the lack of any organized cancer screening in the new independent states of the former Soviet Union, the incidence and mortality rates of cervical cancer are rapidly rising. The objective of this presentation is to outline the most recent data on HPV and related cancers in Latvia provided by the Catalan Institute of Oncology (ICO) Information Centre on HPV and Cancer.

Results

We present the ICO Information Centre on HPV and Cancer Fact Sheet 2017 (2017-07-27) that provides the most recent data on HPV and related cancers in Latvia.

Conclusion

Latvia has a population of 923,264 women ages 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 284 women are diagnosed with cervical cancer and 135 die from the disease. Cervical cancer

ranks as the 5th most frequent cancer among women in Latvia and the 2nd most frequent cancer among women between 15 and 44 years of age. Data is not yet available on the HPV burden in the general population of Latvia. However, in Northern Europe, the region Latvia belongs to, about 4.5% of women in the general population are estimated to harbor cervical HPV-16/18 infection at a given time, and 77.0% of invasive cervical cancers are attributed to HPV 16 or 18.

References

The incidence rate of STD in the Baltic countries is increasing, the average age of patients suffering from STD is decreasing, the specificity of the diagnostic methods used for STD needs to be improved. Women and girls in these NIS countries are conservative in many key characteristics of “high-risk” sexual behavior, such as age at onset of sexual activity, number of partners, and casual sex partners. HPV-positive and HPV-negative groups are clearly distinguished by the same variables identified as the key risk factors of HPV infection and cervical intraepithelial neoplasia (CIN) in Western countries. Surveillance of STD should be intensified where needed. Additional or better-quality data should be collected including reasons for testing, denominator data to estimate positivity rates, diagnostic methods, concurrent STD, sexual orientation, and country of acquisition. More analytical rather than descriptive epidemiology is needed.

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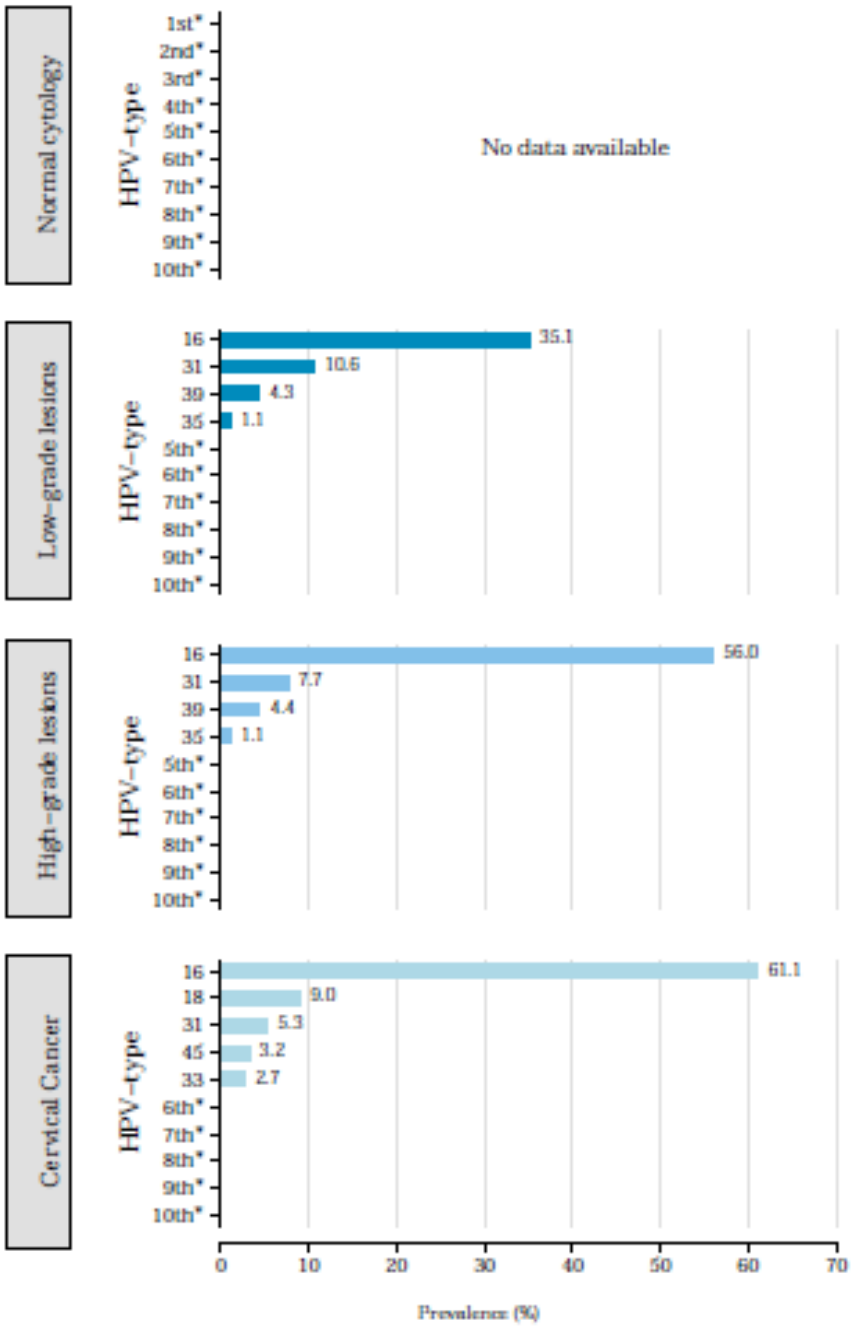
Normal cytology
HPV-type
1st*
2nd*
3rd*
4th*
5th*
6th*
7th*
8th*
9th*
10th*
No data available
Low-grade lesions
HPV-type
16
31
39
35
5th*
6th*
7th*
8th*
9th*
10th*
35.1
10.6
4.3
1.1
High-grade lesions
HPV-type
16
31
39
35
5th*
6th*
7th*
8th*
9th*
10th*
56.0
7.7
4.4
1.1
Cervical Cancer
HPV-type
16
18
31
45
33
6th*
7th*
8th*
9th*
10th*
61.1
9.0
5.3
3.2
2.7
0
10
20
30
40
50
60
70
Prevalence (%)

00609

Epidemiology of oral HPV infection in tonsil tissue

02. Epidemiology and natural history

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Background / Objectives

Human Papillomavirus (HPV), is the causative agent of cancers of the genital tract, including cervical cancer. While cervical cancer prevalence is declining due to effective cervical screening procedures and HPV vaccination programmes, the prevalence of HPV positive Head and Neck Squamous Cell Carcinoma (HNSCC) has been increasing, particularly in young men. HPV is strongly associated with oropharyngeal carcinoma (OPC), a subset of HNSCCs. The prevalence of HPV positive OPC is projected to surpass HPV positive cervical cancers by 2020.

Despite a thorough understanding of the viral life cycle (prevalence, pathogenesis, and persistence) of cervical infection, understanding of the viral infection in the oropharynx is limited; with no screening practices, the trend is for individuals, predominantly male, to present late to clinic with established OPC. Better understanding of the viral lifecycle of HPV within the oropharynx to determine how HPV causes OPC is thus timely. Few studies examine the prevalence of oral HPV in tissues that are known to develop HPV-related OPC; the tonsil.

Results

We will investigate the frequency and pathogenesis of active oral HPV infections in subjects undergoing routine tonsillectomy. qPCR and western blot will be used to assess the viral strain, oncogenic gene and protein expression, and integration status, of HPV within the tonsil. An accompanying questionnaire addressing the individuals' lifestyle choices (sexual behaviour, smoking and alcohol use) will be analysed by generalized linear modelling to examine whether these behaviours influence the prevalence and pathogenesis of oral HPV infection.

Conclusion

This study is only in its early stage, and as such only produced preliminary results. Thus far we have recruited one post-doctoral researcher to lead research work (in post since October), and obtained ethical approval to carry out our work. We have started to collect tonsil samples and questionnaires from subjects at the Royal Derby Hospital (N=30 to date), and are expanding our scope to include two additional nearby hospitals. We have optimised qPCR protocols for the initial HPV screen, targeting the HPV L1 gene, and internal control, targeting subject β-actin.

References

Overall this project will characterise the natural history of oral HPV infection within the disease-relevant tissue of healthy individuals, the tonsils. It will describe the locality of viral infections within the tonsil, and show whether HPV is able to complete its full lifecycle or integrate into the host genome. It will also determine whether gender is associated with the prevalence and pathogenesis of oropharyngeal HPV. As such, this work will begin to assess both the prevalence of oral HPV DNA, and how HPV infection is prognostic for the subsequent development of HPV-OPC.

00063

VERY LOW PREVALENCE OF VACCINE HUMAN PAPILLOMAVIRUS (HPV) AMONG VACCINATED SEXUALLY ACTIVE YOUNG WOMEN: A STUDY IN EASTERN FRANCE

05. HPV prophylactic vaccines

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Background / Objectives

In France, less than 20% of girls remain fully immunized, despite the availability of safe and effective HPV vaccines for over ten years[1]. We estimated the overall prevalence and distribution of HPV in vaccinated, sexually active young eastern French vaccinated women who were screened for cervical cancer by cytology and HPV testing.

Results

High-risk HPV (HR-HPV) prevalence, genotype-specific prevalence and extent of multiple infections were assessed in 125 cervical samples from females with available vaccine data using hc2 assay and INNO-LiPA assay in our regional university hospital referral center in France. HPV status was analyzed in accordance with cytological data.

Conclusion

In our series, mean age was 23 years (±3.3). Overall prevalence of HR-HPV was 52% and was correlated with the lesion grade. The diversity of HPV genotypes was broad. The overall prevalence of genotypes covered by the quadrivalent vaccine was

low (5.9%); with 4.2%, 0%, 0.8% and 0.8% for HPV 16, HPV 18, HPV 6 and HPV 11 respectively. Single HR-HPV infections were identified in 11%, 21% and 47% of women with NILM, ASC-US/-H and LSIL respectively. Multiple infections with HR-HPV were detected in 28% of the specimens; only 24.5% of women with NILM presented infections with 2 HR-HPV genotypes or more, vs 28% of women with ASC-US/-H and 35% of women with LSIL.

References

Among HPV-vaccinated young women, HR-HPV are detected at a high rate, and an association with the grade of cytological abnormalities was observed. However, HPV 16 and 18, both targeted by the vaccines, are remarkably rare among young French women since program implementation.

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00106

IMPACT AND EFFECTIVENESS OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE ON ORAL AND ANAL HPV INFECTIONS AND RECURRENT RESPIRATORY PAPILLOMATOSIS

05. HPV prophylactic vaccines

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Background / Objectives

The real-world impact and effectiveness of quadrivalent HPV vaccination (4vHPV) on cervical HPV infection and disease was previously assessed [1]. Our aim was to review the evidence related to impact and effectiveness of 4vHPV on endpoints not previously assessed: oral and anal HPV infections and recurrent respiratory papillomatosis (RRP).

Results

Medline and Embase were searched for observational studies (published before April 12, 2018) evaluating real-life benefits of 4vHPV. Impact was defined as population prevented fraction of abnormalities by comparing risk of specified endpoints before and after vaccination program introduction or trends over time. Effectiveness was assessed as proportion of prevented endpoints, comparing vaccinated and unvaccinated individuals.

Conclusion

Data was extracted from 8 studies (Table 1), with 88% reporting effectiveness measures. Studies included both women and men, from the age of 12, with the

exception of the RRP study which was in children between 0-14 years of age. Studies came from Australia (n=1, RRP), and the US (n=7, anal [n=4] and oral [n=3]). Vaccination reduced vaccine-type (VT) anal infection by >60%, and VT oral infection by 80-100%. Variability in results was likely due to heterogeneity of the studies (populations; cohorts; sexual preferences; vaccine coverage rates; time since start of vaccination program). The incidence of RRP was reduced by 87% 4 years after introduction of vaccination. [Legend to table: E/I – Effectiveness/Impact; M/F – male/female; MSM – men having sex with men; VT-HPV – vaccine-type HPV; HGAIN– high-grade anal intraepithelial neoplasia; RRP - recurrent respiratory papillomatosis].

References

Reductions in HPV infections and lesions, occurring in both genders, are becoming increasingly evident. This indicates that the vaccine prevents infections and lesions in all organs affected by HPV and provides additional support for 4vHPV benefits.

References

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Study	Endpoint	E/I	M/F (age)	Measure	% reduction
Schlecht, PLoS One 2012	Anal infection	E	F (12-19)	VT-HPV infections (3 doses vs non-vac)	62.0
Schlecht, JID 2016	Anal infection	E	F (12-19)	VT-HPV Incidence rate ratio (vac vs non-vac)	64.0
Swedish, CID 2012	Recurrent HGAIN	E	MSM (18+)	incidence rate (vac vs non-vac)	35.0
Swedish, PloS one 2014	Anal condyloma	E	MSM (26+)	incidence rate (vac vs non-vac)	49.3
Schlecht, PLoS One 2012	Oral infection	E	F (12-19)	VT-HPV infections (3 doses vs non-vac)	79.8
Kahn, STD 2015	Oral infection	E	MF (12-24)	VT-HPV infections (3 doses vs <3 doses)	100.0
Chaturvedi, JCO 2018	Oral infection	E	MF (18-33)	all HPV infections (vaccinated vs non-vac)	27.4
Novakovic, JID 2018	RRP	I	MF (0-14)	Incidence post-vac (2016) vs pre-vac (2012)	87.5

00256

PREVALENCE OF HPV INFECTION AND HYPOTHETICAL EFECT OF THE NONAVALENT VACCINE IN WESTERN HUESCA (SPAIN)

05. HPV prophylactic vaccines

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Background / Objectives

Cervical cancer is one of the most common cancers all over the world. In developed countries is health care problem, but with a relative low mortality due to the vaccination and the screening. The available vaccines includes 2, 4 or 9 HPV types. Our aim is to estimate the porcentage of infections and high grade lesions that could be avoided with the 9 types vaccine Gardasil 9®.

Results

The target population were women between 25 to 65 years in our regional heath area. The period of study was from May 2012 to June 2018, in this time the screening program was based on HPV. Cytologies were collected with Thinprep®. HPV test was performed with COBAS 4800®. The majority of positive cases to not 16/18, and randomly some of the positive 16/18, were genotyped with Clart HPV4®. The porcentage of avoidable infection with Gardasil9® was calculated. The agreement between both technologies was calculated.

Furthermore we selected all the colposcopy biopsies from February 2016 to June 2018 with HSIL o carcinoma and with genotyping on the cytology with Clart HPV4®. The porcentages of avoidable HSILs and carcinomas with Gardasil9® and coinfections were calculated. The agreement between cytology and lesions was calculated.

Conclusion

In the time period has been perfomed 19669 HPV test, being positive 2881 (prevalence of 14,65%). From them 1628 (56.51%) were genotyped with Clart HPV4 ®. The agreement to 16, 18, and other high risk types were 96.3, 92.1 and 95.6%, respectively. Hypothetically 66,65% of the HPV infections could be avoided with Gardasil9® .

Due to the screening program from February 2016 to June 2018 521 colposcopy biopsies has been made, with 177 (33.97%) HSILs and 12 (2.30%) carcinomas. In 171 (90.47%) there was a genotyped in previous cytology and later the biopsy was genotyped with Clart HPV4 ®. With Gardasil9 ® could have been avoided 145 HSILs or carcinomas (84,79%), including the 5 carcinomas of the series. In 39 of the lesions (26,90%) we found coinfection with more than one HPV type. The agreement between cytology and biopsy was 87.6%, with a complete and partial agreement of 34.3 and 53.3%, respectively

References

The agreement between both technologies is appropiate with rates higher tan 90%. It means that both are valid and the election will depend on the characteristics and the organization of each service.

Gardasil 9® could avoid 2/3 HPV infections and around 85% of the HSILs and carcinomas.

The HPV coinfection is a relative feature more than an exceptional phenomenon.

There is a relative good agreement between cytology and biopsy genotyping.

00348

Prevention of HPV-associated recurrence of CIN3: the experience of vaccination against HPV

05. HPV prophylactic vaccines

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Background / Objectives

Improvement of the treatment results of HPV CIN III after the initial treatment through vaccination against HPV considering the proven etiological role of the papillomavirus in cervical oncogenesis.

Results

The research is based on the analysis of clinicomorphological data and the results of the HPV test performed on 50 HPV CIN III infected persons from 22 to 46 years of age. High-risk HPV genotypes were identified with Hybrid Capture II method in all clinical observations whereby types 16/18 had the highest S.G. (more than 70%), in all other cases - types 45 (7%), type 33 (4,5%), type 35 (3,8%), type 56 (2,6%), and type 58 (0,2%). Suprathreshhold concentration of the HPV DNA (concentration 100 k genocopies/ml or 1mg/ml) was identified in all the research samples. During the first stage of treatment surgical and radio-wave cervical cone biopsy was performed on all patients; at the second stage in order to eradicate HPV photodynamic therapy of the cervical stump was performed with simultaneous vaccination (Gardasil) to prevent recontamination and development of HPV CIN III exacerbation. Cytological cervical stump swabs were performed within the established times set for the given incidence of tumorous changes in the cervical area. HPV test was performed once a year.

Conclusion

In all clinical test the HPV test turned out to be negative during the whole period of observation, cytological and colposcopical tests showed absence of atypical changes in the cervical epithelial tissue, subclinical and clinical evidence of HPV infection.

References

All clinical laboratory negative tests received upon check-up of women infected with HPV CIN III after the initial treatment show that ,considering the proven etiological role of HPV in cervical oncogenesis among the women of sexually active age and the promiscuous men, it is necessary to have activities directed at prevention of recontamination of high-risk HPV. Vaccination after the initial HPV treatment prevents HPV associated CIN III exacerbation. This approach is scientifically justified and is recommended for practical application in the health care services system.

00488

PREVALENCE AND GENOTYPING OF HPV IN A PORTUGUESE VACCINATED POPULATION

05. HPV prophylactic vaccines

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Background / Objectives

HPV is the most common sexually transmitted disease and is responsible for 99.7% of cervical cancer. Cervical cancer is the fourth most frequent cancer in women and is the second most frequent cancer among portuguese young women aged 15 to 44 years old, making prevention a major objective of Public Portuguese Health.

Prophylactic HPV vaccines protect against a majority of HPV infection, which are associated with anogenital pre-malignant diseases and cancers in women and anogenital intraepithelial neoplasia and cancers in men and a subset of head and neck cancers.

Quadrivalent HPV vaccine is included in the Portuguese National Immunization Program (PNV) since 2008 and a vaccination rate higher than 85% has been achieved.

The main objective of this study is to characterize HPV genotypes in a vaccinated young woman who were referred to our department for abnormal pap smear.

Results

Retrospective study of women born after 1991, vaccinated with quadrivalent vaccine and referred to our department for abnormal cervical cytology and/or genital warts between 2013 and 2018.

Conclusion

Sixty-two women with mean of age was 21.1 ± 2.0 [16-25] years old were included.

In our sample, 58.9% of women had started their sexual life prior to vaccination and 72.3% had have more than one sexual partners. Ten women (16.1%) had already become pregnant at least once, and 2 had an abortion. Twenty-eight women were smokers (45.2%).

Two women had genital warts and the remaining 60 had abnormal results in cervical cytology: 51.6% LSIL; 38.7% ASCUS; 3.2% HSIL; 1.6% AGC; 1.6% AIS.

HPV genotyping was performed using COBAS test. None were positive for HPV 16 or 18. Twenty women were positive for other high-risk HPV (HR-HPV) and of whom 47.1% were positive for p16/Ki 67 identified by the CINtec PLUS test.

References

This study highlights the importance of cervical cancer screening in vaccinated women since not all HR-HPV genotypes are covered by the vaccine. It is therefore important to detect and surveil anogenital pre-malignant lesions in this population.

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00496

A SYSTEMATIC LITERATURE REVIEW UPDATE OF THE IMPACT AND EFFECTIVENESS OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE ON CERVICAL ABNORMALITIES

05. HPV prophylactic vaccines

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Background / Objectives

The real-world impact and effectiveness (VE) of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease was previously assessed in 2016, ten years after 4vHPV licensure [1]. Our aim was to update the evidence related to impact and VE of 4vHPV on cervical abnormalities, including cytological abnormalities and histologically-confirmed cervical intraepithelial neoplasia.

Results

Medline and Embase were searched for observational studies evaluating real-life benefits of 4vHPV (March 1, 2016 – April 12, 2018). Reviews, conference, disease-burden, modeling, awareness, clinical trial studies and studies with mixed 4vHPV and 2vHPV were excluded. Impact was defined as population prevented fraction of abnormalities by comparing population before and after vaccination program or trends over time and VE as proportion of prevented abnormalities comparing vaccinated and unvaccinated individuals.

Conclusion

Of 1533 publications identified in the last 2 years, 8 studies (5 impact, 3 VE) from Australia, Canada and US provided data related to 4vHPV and cervical abnormalities, compared to 16 studies in previous review. Significant impact on high-grade (HG) cervical abnormalities in vaccine era were observed especially among females 15 to 24 years of age with estimated 6%-20% annual percentage declines. The impact of vaccination on reductions of histologically confirmed cervical lesions

among women 25-29 years, who were aged 18-26 years at vaccination, was newly reported in one study. VE of 50%-62% for HG and of 28%-73% for low-grade cytological cervical abnormalities were reported.

References

The impact and effectiveness of 4vHPV on reductions of cervical abnormalities is becoming increasingly evident, including first signs of a decline among 25-29 years old women who received catch-up vaccination.

References

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00538

ASSOCIATION BETWEEN PAP ABNORMALITIES AND HPV INFECTION IN PARTICIPANTS IN HPV VACCINE CLINICAL TRIALS

05. HPV prophylactic vaccines

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Background / Objectives

Few studies have reported the burden of Pap abnormalities associated with the specific HPV types targeted by HPV vaccines. The purpose of this analysis is to estimate prevalence of HPV anogenital infection, by baseline Pap results, in participants of 3 worldwide trials of the quadrivalent HPV vaccine (placebo and vaccine groups, FUTURE I, II, III), and to estimate incidence of Pap abnormalities by HPV infection status at enrollment (placebo only, FUTURE I, III).

Results

Among 16,949 young women (YW) age 15-26 years (FUTURE I, II) and 3,674 adult women (AW) age 24-45 (FUTURE III), HPV prevalence (measured with PCR for 14 HPV types) was estimated at enrollment for women with:

-atypical squamous cells of undetermined significance (ASC-US) (n=781 YW, 115 AW),
-low-grade squamous intraepithelial lesion (LSIL) (n=993 YW, 115 AW), and
-high-grade squamous intraepithelial lesion or atypical squamous cells- cannot exclude HSIL (HSIL/ASC-H) (n=157 YW, 30 AW).

Cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) over 4 years (placebo only), by baseline HPV status, was estimated for 1,481 (YW) and 1,701 (AW).

Conclusion

Prevalence of any 9-valent (9v) vaccine type (6/11/16/18/31/33/45/52/58) among women with ASC-US, LSIL, or ASC-H/HSIL at enrollment was 47%, 67%, and 89%, respectively (YM), and 29%, 55%, and 93%, respectively (AW). Prevalence of any non-vaccine type (35/39/51/56/59) among women with ASC-US, LSIL, or ASC-

H/HSIL was 32%, 64%, and 47%, respectively (YM), and 24%, 54%, 38%, respectively (AW). Over 48 months, cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) among women with any high-risk 9v HPV type at enrollment was 8% (YW) and 6% (AW); cumulative incidence among women with no measured HPV infection at enrollment was 2% (YW) and 0.4% (AW).

References

While the 9-valent vaccine will substantially reduce Pap abnormalities associated with HPV types that cause 90% of cervical cancers, non-vaccine HPV types also contribute to Pap abnormalities. These findings underscore the need for vaccination to protect against 9 HPV types, as well as the ongoing need for cervical cancer screening.

00029

Efficacy of HPV Vaccine in preventing of increasing cervical lesion in abnormal Pap test

06. HPV therapeutic vaccines

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Background / Objectives

Aggressive cervix cancer is one of the prevalent gynecologic cancers in developing countries; by conducting Pap smear tests and malignancy background tests and treatment, it could be prevented. On the other hand, the majority of Cervix cancers are the result of HPV virus. HVP virus is the most widespread virus which is transferred through intercourse. In developing countries, HPV vaccination is conducted to all women of 9 to 26 years of age, and in all men too. Nevertheless, with respect to the fact that this Vaccine is costly and limited in our country, and most studies have investigated the preventing effects of this vaccine, so we want to assess efficacy of HPV Vaccine in preventing of increasing cervical lesion in patient with abnormal Pap smear test.

Results

In this study, 242 women that had various grades of infection(CIN1, 2, 3) which referred to a women's clinic for determine the effectiveness of HPV vaccine, by signing a consent were studied. Pregnant women and women with severe allergies were excluded. The control group comprised of 104 (42.7%) women which did not receive the treatment. In the Experimental group, 35 women (14.4%) received 2 vaccinations, and 103 (42.3) received 3 vaccinations. Throughout the 2 years, all patients were treated according to the protocol; in addition, the results of the cervix inspections were documented. The collected data were analyzed using SPSS, chi-square and fissure exact tests.

Conclusion

The mean age of the samples were 32.59 ± 4.85, that was significantly differences (p=0.022) between groups. At the end of the study, the total number of patients that

returned back to normal condition comprised of those who were received the Vaccinations in comparison with control group was significantly difference (p-value= 0.022, 0.033, 0.035) . Also efficacy of vaccine in group with 3 dose vaccinations was larger than group with 2 dose vaccinations in comparison with control group.

References

this study showed that a quadrivalent HPV vaccine prevents of increasing cervical lesion in patient with abnormal Pap test.

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00224

THERAPEUTIC HUMAN PAPILLOMAVIRUS VACCINES IN HEAD AND NECK CANCER: A SYSTEMATIC REVIEW OF CURRENT CLINICAL TRIALS

06. HPV therapeutic vaccines

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Background / Objectives

This systematic review provides an overview of the current clinical trials investigating therapeutic vaccines in HPV+ head and neck cancer, and discusses future directions of therapeutic vaccine therapy.

Results

In PubMed, EMBASE, Cochrane and clinicaltrials.gov, a systematic search was conducted for clinical trials investigating therapeutic vaccines. We included studies initiated between 2000 and 2018 with patients diagnosed with HPV+ head and neck cancer, and extracted data on type of vaccine therapy, adverse events, immunogenicity and clinical outcome measures as tumor response, progression free survival and overall survival.

Conclusion

We identified 11 studies (n=376 patients) initiated between year 2005 and 2017. Four studies (n=34) presented temporary results, in patients with incurable, recurrent loco-regional or distant metastatic disease, indicating a positive immune response with 74 % (n=25/34 patients) having elevated antibody, IFN-γ and/or T-cell response, respectively. Five studies presented data on the vaccines' safety profile, demonstrating predominantly grade 1 and 2 toxicity. Three studies evaluated the clinical outcome – one study showed no complete or partial response, one study demonstrated stable disease as best tumor response in 64% (9/14 patients) and one study showed a 33% overall response rate; one patient with complete response and seven patients with partial response.

References

Treatment with therapeutic vaccines is a promising and seemingly safe strategy for HPV+ head and neck cancer patients. But so far there are not enough data to make any further conclusions, and especially clinical outcome measures and tumor response to the vaccines are missing.

00043

Clinical significance of HC2 test results in Grey Zone range used in Slovenian Cancer Screening Program ZORA

08. HPV testing

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Background / Objectives

The Slovenian national screening program ZORA uses Hybrid Capture 2 High-Risk HPV DNA assay (HC2, Qiagen, Hilden, Germany) as a triage method for women with low-grade cytology abnormalities and as a test of cure after CIN treatment. Due to reported limited analytical accuracy of HC2 near the cut-off value 1.0 RLU/CO, manufacturer recommends that specimens collected in standard transport medium (Qiagen) whose results fall near but bellow 1.0 RLU/CO should be repeated or retested with an alternate testing method. Based on these recommendations our laboratory at Oncology institute Ljubljana has implemented an internal RLU/CO range between 0.7 and 2.0 RLU/CO, called “Grey Zone”, in which we repeat HC2 assay. The aim of this study was to determine the clinical relevance of the Grey Zone in our laboratory involved in the Slovenian cervical screening program.

Results

In total 594 women (aged from 20 to 65 years, 44.3 on average) referred to colposcopy were included in the study. Biopsy was performed in case of abnormal colposcopy result and 162 CIN2+ cases were detected within one-year follow-up. We have determined the percentage of women with negative, Grey Zone and positive HC2 test results. We have compared three different Grey Zone ranges. Our internal Grey Zone (0.7-2.0 RLU/CO), Grey Zone proposed at the Institute of Microbiology and Immunology, Slovenia (0.4-4.0 RLU/CO) and by the manufacturer (Qiagen) for PreservCyt medium (1.0-2.5 RLU/CO). We have also calculated sensitivities and specificities of HC2 at different cut-off values.

Conclusion

Four point five % of participating women had HC2 results within our Grey Zone range (0.7-2.0 RLU/CO), 10.8% within range 0.4-4.0 RLU/CO and 3.7% within range 1.0-2.5 RLU/CO. The calculated sensitivities and specificities of HC2 at different RLU/CO cut-off values are presented in Table 1.

Table 1. Sensitivity and specificity of HC2 results for CIN2+ at different cut-off (RLU/CO)

RLU/CO	Sensitivity (95% CI)	Specificity (95% CI)
0.4	95.1% (91.4-98.1%)	56.7% (51.9-61.3%)
0.7	94.4% (90.7-97.5%)	60.6% (56.0-65.3%)
1.0	93.8% (90.1–97.5%)	63.2% (58.6–67.6%)
2.0	93.2% (89.5-96.9%)	66.4% (61.8-70.8%)
2.5	91.4% (87.0-95.7%)	67.6% (63.0-72.0%)
4.0	89.5% (84.6-93.8%)	69.4% (65.0-73.8%)

References

Increase of cut-off value from lower to upper bound of 0.7-2.0 RLU/CO zone results in a decrease of sensitivity for 1.2% and increase of specificity for 5.8%. On the contrary in the 0.4-4.0 zone, sensitivity decreases below 90.0% with 12.7% increase of specificity. To determine the clinical meaning of Grey Zone range and the value of the cut-off additional studies are needed, which will evaluate the risk for CIN2+ in Grey Zone range on the general population.

00107

PRELIMINARY EVALUATION OF THE HIGH+LOW PAPILLOMASTRIP ASSAY WITH COLLI-PEETM COLLECTED UCM PRESERVED URINE.

08. HPV testing

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Background / Objectives

The High+Low PapillomaStrip test (Operon) allows qualitative detection of 37 human Papillomavirus types in DNA samples from cervical smears or biopsies. The aim of this pilot study is to determine whether the PapillomaStrip assay is compatible with self-collected UCM preserved first-void urine samples.

Results

Twenty-two self-reported HPV positive women provided a Colli-PeeTM (Novosanis) collected first-void urine sample, on two subsequent days. Samples were collected at home. The collection tubes prefilled with UCM preservative were sent by mail to the University of Antwerp. 4 ml of urine/UCM mixture was concentrated using an ultrafiltration membrane and extracted with an easyMAG semi-automated DNA extractor (bioMérieux). Subsequently, the DNA extract was analysed using the Riatol qPCR HPV genotyping assay (AML) and the High+Low PapillomaStrip assay. To provide sufficient volume for the Riatol qPCR assay the DNA extract was diluted (35µl DNA extract with 40µl elution buffer).

Conclusion

We observed a 100% agreement between the PapillomaStrip assay outcomes of the first and second day when expressed as high-risk (hr)HPV positive or negative. Five women were negative and 17 were positive for both samples. Also at the level of detected genotypes a very good agreement was observed. When comparing the hrHPV results generated by the Riatol qPCR and the PapillomaStrip assay, a kappa coefficient of 0.82 (CI 95%: 0.64–1.00) was observed. 31 and 10 samples gave respectively concordant positive and negative results. Three samples were negative

for Riatol qPCR and positive for the PapillomaStrip. These three samples also yielded a positive outcome using other commercial HPV assays.

References

These preliminary results confirm that the High+Low PapillomaStrip test is compatible with self-collected UCM preserved first-void urine. Confirmation of performance by testing larger series of first-void samples in a clinical setting is warranted.

00143

HPV and CMV infection among HIV-positive women in some countres of Eastern Europe and Central Asia

08. HPV testing

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Background / Objectives

The frequency of detection of HPV varies greatly depending on the region of residence of the woman. Also HIV-infected women have a higher risk of HPV infection than HIV-negative women, and a higher risk of persistence and malignancy.

Objective: to study the prevalence of human papillomavirus of high carcinogenic risk (HPV HCR) and cytomegalovirus (CMV) in HIV-infected women in some countries of Eastern Europe and Central Asia.

Results

647 HIV-infected women from Russia, Belorussia, Armenia, Azerbaijan, Tajikistan and Kyrgyzstan were examined from September 2017 to December 2017. All women were tested for HPV-test with the determination of 14 types of HPV HCR (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and CMV.

Conclusion

Among the 647 women surveyed, mostly young people (under 40 y-s) predominated. As a result of the HPV-test, 265 (41%) of HIV-infected women were diagnosed with HPV HCR. All 14 HPV HCR genotypes were diagnosed in 28-48% HIV-positive women, depending on the region: Armenia - 39%, Azerbaijan - 43%, Belarus - 28%, Kyrgyzstan - 46.5%, Tajikistan - 37.8%, Russia (Samara) - 48%.

In 208 (32.1%) of HIV-infected women were diagnosed with CMV infection. 105 (16.2%) of HIV-infected women had co-infection with HPV + CMV. There are differences between the group of HIV-infected women with co-infection with HPV + CMV and a group of HIV-infected women with HPV without CMV ($\chi 2 = 11.495$, $p < 0.001$).

References

HIV-infected women often have a combination of HPV infection and CMV infection. The data obtained should be used in the compilation of algorithms for cervical screening in HIV-infected women

00153

Ethiopathogenesis of adenocarcinoma in situ cervicis (AIS) - is there a difference in relation to squamous intraepithelial lesions (SIL)?

08. HPV testing

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Background / Objectives

AIS presents a rare histopathological form of cervical cancer. This histological type is still an enigma in the understanding of etiopathogens.

The aim of this study was to:

1. Determine whether is there a difference in the positivity of human papilloma virus (HPV), as well as the type of HPV in SIL and in AIS?

2. To determine if there is a difference in the epidemiology of SIL and AIS in relation to heredity and sexual behavior?

3. Determine whether contact and irregular vaginal bleeding is more common in SIL or AIS?

Results

At the Clinic for gynecology and obstetrics, Clinical center Nis, Serbia, within the internal scientific project of the Faculty of Medicine, University of Nis, was conducted a prospective study which involved the first 120 patients who were operated for intraepithelial and invasive changes in the cervix since January 2017. In all of the operated patients, HPV typing was done with a PCR method, and the epidemiological data were taken with a survey, which was filled immediately prior to operative treatment.

Conclusion

Of the 120 operated patients, AIS was present in 14 (11, 47%). In contrast to squamous lesions that were HPV negative in only 7,4% of subjects, AIS patients were more often HPV negative at 28.57%. As for positivity in relation to the type of virus in AIS, it is more often HPV 18 (14,28% : 5.5%). Of the other associated HPV types in AIS are detected HPV types: 39, 45, 51 and 56.

Epidemiological data from AIS and SIL showed that AIS patients in relation to the patients with AIS have a high percentage of overwhelming family history of gynecological localization (71,42% : 27,7%). Also, patients with AIS compared to SIL patients are more regularly smokers (71,42% : 46,29%) and have more often than one sexual partner (71,42% : 31,48%).

The anamnestic data on contact bleeding into sexual intercourse was more common in AIS patients (57.14% : 14.28%) and given that AIS cytological findings were falsely negative in 85%, it was precisely the contact bleeding that helped in diagnosing.

References

Adenocarcinoma of the cervix differs in ethiepidemiology from squamous lesions of the same localization. This histological type is more often HPV negative or positive for HPV 18 and some of the HPV types that are more commonly encountered in squamous lesions (39, 45, 51, 56). In relation to epidemiology, this histological type is more often associated with the inheritance, smoking and having more sex partners.

Anamnestic, in relation to squamous lesions, domination of contact bleeding data could be of great diagnostic benefit, given the fact that cytology is low sensitivity in the diagnosis of cervical adenocarcinoma.

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00262

HPV TEST AND IMPROVEMENT IN CYTOLOGY EFFICENCY IN WESTERN HUESCA (SPAIN)

08. HPV testing

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Background / Objectives

Human Papilloma Virus (HPV) is the most common sexually transmitted disease. There are more than 100 HPV types, 14 of them with a high oncogenic potential and relationship with cervical cancer.

HPV screening is based on its detection with a high sensitivity. It reduces the number of Papanicolau smears (Pap smears) avoid them if HPV test is negative.

We show the differences in cytology between cytology, cotesting and HPV test screening protocols

Results

The target population were women from 25 to 65 years old in our regional heath area. Cytologies were collected with Thinprep®. HPV was performed with COBAS 4800®. Between 2010 to 2013 the screening was based on cytology, beginning at 21. From January 2014 to January 2016 the screening was based on cotesting, beginning at 25 with cytology and cotesting with HPV from 30 to 65. From February 2016 to June 2018 the screening has been based on HPV, beginning at 25 with cytology and with HPV test from 30 to 65, the Pap smear was only performed after an HPV positive test.

Conclusion

From January 2010 to June 2018 has been performed 33293 Pap smears with 1986 (5.96%) atypias and 122 (0.37%) HSIL. It means that 16.76 and 272.89 Pap smears

were necessary to get one atypia or HSIL, respectively. At the same time were performed 1068 biopsies, being 377 (35.30%) positive to HSIL. It implies that 88.31 Pap smears were necessary to diagnose one histological HSIL.

In the cytology period there were 19482 Pap smears with 972 (4.99%) atypias and 38 (0.19%) HSIL. It supposes that 20.04 and 512.68 Pap smears were necessary to get one atypia or HSIL, respectively. At the same time were performed 233 biopsies, being 69 (29.61%) positive to HSIL. It means that 282.35 Pap smears were necessary to diagnose one histological HSIL.

In the cotesting time there were 10046 Pap smears with 480 (4.78%) atypias and 28 (0.28%) HSIL. It supposes that 20.93 and 358.79 Pap smears were necessary to get one atypia or HSIL, respectively. At the same time were performed 314 biopsies, being 119 (37.90%) positive to HSIL. It means that 84.42 Pap smears were necessary to diagnose one histological HSIL.

In the HPV screening has been performed 3765 Pap smears with 534 (14.18%) atypias and 56 (1.49%) HSIL. It supposes that 7.05 and 67.23 Pap smears has been necessary to get one atypia or HSIL, respectively. At the same time were performed 521 biopsies, being 189 (36.27%) positive to HSIL. It means that 19.92 Pap smears were necessary to diagnose one histological HSIL

References

HPV has improved the cytological efficiency in cervical cancer screening:

Reducing the absolute number of Pap smears by 70%.
Decreasing the number of Pap smears to diagnose a HSIL in colposcopy biopsies.

00268

VALIDATION OF A COMMERCIAL HPV TESTING ASSAY TO DETECT HPV16 IN ANAL CYTOLOGY SPECIMENS FROM A HIGH-RISK PATIENT POPULATION

08. HPV testing

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Background / Objectives

Detection of human papillomavirus type 16 (HPV16) in anal cytology specimens may be used for risk profiling for high-grade anal dysplasia and carcinoma. To validate the Cervista HPV16/18 assay, a commercial availalble HPV assay, in detecting anal HPV16 infection, we compared Cervista HPV16/18 and HPV16 type–specific PCR assays in 77 anal specimens collected from high-risk patients.

Results

We retrospectively searched our institutional databases for patients with anal HSIL or carcinoma or cervical intraepithelial neoplasm grade 2 or 3 (CIN2/3) and carcinoma who underwent anal cytology and anal Cervista HPV16/18 testing at our institution from 2016 to 2017. The Cervista HPV16/18 assay (Hologic Inc., Bedford, MA, USA) was performed followed by HPV16 PCR testing. Patients underwent anal cytology, high-resolution anoscopy and/or biopsy at the time of HPV testing and/or at subsequent visits. Results for the Cervista HPV16/18 and HPV16 PCR were compared and correlated with the concurrent/follow-up anal cytology and biopsy results. The kappa efficiency test and the Fisher exact test were used to compare the variables.

Conclusion

A total of 77 patients met inclusion criteria for the study and included 12 men and 65 women. The mean age was 53 years (range, 27-87). Of the 77 patients, 28 (36%) had history of anal dysplasia/carcinoma (1 HSIL, 5 AIN2, 15 AIN3, 7 carcinoma). The concurrent or follow up anal cytology and biopsy results showed 17% (13/77) of patients had high-grade anal dysplasia/carcinoma (7 HSIL, 5 AIN3, 1 carcinoma).

The concordance between Cervista HPV16/18 and HPV16 PCR results was 78% (60/77) with moderate agreement (kappa=0.461) (Table 1). HPV16-positive rate was higher by the HPV16 PCR (34%, 26/77) than by the Cervista HPV16/18 (21%, 17/77), but the difference was not significant (P=0.150). The significantly higher HPV16-positive rate by HPV16 PCR was observed only in patients with a negative anal Pap cytology/biopsy result (Table 2). The Cervista HPV16/18 assay showed the same sensitivity (50%) as the HPV16 PCR but higher specificity (84.1% vs. 69.8%) for anal HSIL/AIN2/3/carcinoma.

References

The Cervista HPV16/18 assay is comparable to HPV16 PCR assay and a valid testing assay to detect HPV16 in anal cytology specimens from high-risk patients for risk profiling. In patients with negative anal cytology/biopsy results, the clinical significance of the higher HPV16-positive rate by HPV16 PCR that is mostly due to low HPV16 copy numbers is unclear. Further studies are needed to delineate the risk and recommended follow-up of patients with positive HPV16 testing.

Table 1. HPV16 testing by Cervista HPV16/18 and HPV16 type–specific PCR assay in anal Pap specimens (n=77)

	PCR HPV16 +	*PCR HPV16 -*	*Total*
Cervista HPV16 +	*13*	*4*	*17*
Cervista HPV16 -	*13*	*47*	*60*
Total	*26*	*51*	*77*

Kappa=0.461; Agreement: 77.9%, (60/77)

Table 2. HPV16 test results by Cervista HPV16/18 and HPV16 type–specific PCR assay stratified by anal Pap cytology/biopsy result (n=77)

Anal Pap/Biopsy (Case No.)	Cervista HPV16/18+ (%)	HPV16 Type–specific PCR+ (%)	P-value
NILM (38)	4 (11)	13 (34)	*0.026*
ASCUS/ASC-H/ LSIL/AIN1 (25)	6 (24)	6 (24)	*1.000*
HSIL/AIN2/3/ Carcinoma (14)	7 (50)	7 (50)	*1.000*
Total (77)	17 (22)	26 (34)	*0.150*

NILM: no intraepithelial lesion or malignancy; ASCUS: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells, cannot exclude high-grad squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion

00298

EVALUATION OF P16INK4A AND KI-67 EXPRESSION AND ASSOCIATION WITH HUMAN PAPILLOMAVIRUS INFECTION IN CARRIERS OF PENILE CANCER IN BRAZIL

08. HPV testing

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Background / Objectives

Penile carcinoma (PC) is a rare disease that affects people of all ages and is considered a public health problem. Poor hygiene, phimosis in adult life, and human papillomavirus (HPV) infection are risk factors for penile carcinoma. The lack of specific predictors that identify inguinal micrometastases could decrease the indication of a large number of unnecessary inguinal lymphadenectomies. The search for possible markers to identify the increased risk of inguinal metastasis has been the subject of research. **Objetives:** This study aims to determine the prevalence and genotypes of HPV in cases of penile carcinoma in Central Brazil, to evaluate the expression of the proteins associated with tumor suppression ($p16^{INK4a}$) and cell proliferation (Ki-67) in these neoplasms and to associate with clinicopathological findings of PC cases in Central Brazil - Goiás.

Results

Methods: Retrospective study of 183 individuals with Penile carcinoma undergoing treatment at Hospital Araújo Jorge, Goiânia-GO iin Cenral Brazil , from 2003 to 2015. The paraffin-embedded samples had DNA-HPV detected and genotyped by the INNO-LiPA kit, specific for paraffin-embedded tissues. Expression of p16INK4a and Ki-67 was evaluated by immunochemical (IHC) using the immunoperoxidase method.

Conclusion

Results: The prevalence of HPV-DNA in penile carcinoma was 30.6% (95% CI: 24.4-37.6), high-risk HPV 24.9% (95% CI: 18.9-31.3), that 62.5% of the samples were HPV-16. HPV status did not change the SCE in five years. Expression of $p16^{INK4a}$ was associated with HPV infection (p = 0.001), Ki-67 immunolabeling was associated with inguinal metastasis (p = 0.0002) and lymphovascular invasion (p <0.0001). There was no difference in SCE over five years between individuals with high and low risk HPV infection and between expression of $p16^{INK4a}$(p = 0.07) and Ki-67 (p = 0.542).

References

Conclusion: The study showed that 80.3% of the genotypes identified in CP are immunopreventable by the quadrivalent or nonvalent anti-HPV vaccine. Expression of p16INK4a by IHC in penile tumors can be used as a marker of high-risk HPV infection. Ki-67 expression was associated with the characteristics of greater tumor aggressiveness, although there was no association with worse survival

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00351

HPV COLONIZATION IN CERVICAL SECRETIONS VERSUS INFECTION IN CERVICAL CANCER TISSUE

08. HPV testing

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Background / Objectives

Despite of HPV colonization in cervical secretions persistent HPV infection with cervical cancer risk develops to a small percentage of women. With increased certain HPV type persistence in organism, chances for virus to be cleared out spontaneously decreases, and chances to diagnose precancerous condition increases.

Objective. To determine and compare high risk HPV types in cervical secretions and tissue in women with cervical cancer.

Results

In this study 29 women with diagnosed cervical cancer (CA) during 2017 - 2018 years in hospital of Lithuanian University of Health Sciences were involved. For all women 2 samples for Human Papillomavirus (HPV) genotyping were taken: liquid based cytology medium (LBCM) and tissue biopsy. HPV DNA was isolated using commercial QIAamp DNA (Qiagen, USA) kit. For DNA amplification polymerase chain reaction method was used. HPV genotype was detected using hybridization and visualisation AmpliSens PCR kit (Bratislava, Slovakia).

Conclusion

High risk (HR) HPV was detected in 96.6% (n=28) of tested women with CA in both samples groups. One HR HPV type was detected in 58.6% (n=17), two in 27.6% (n=8) and three in 10.3% (n=3) cases in LBCM. In tissue biopsy one HR HPV type was detected in 89.7% (n=26) and two in 6.9% (n=2) cases. More than one HR HPV type was found in LBCM 39.3% (n=11), in tissue biopsy, respectively 6.9% (n=2). We

have found trends that more often HPV16 and HPV18 types alone were detected in tissue biopsy compare to LBCM (82.8%, n=24 and respectively 58.6%, n=17; p=0.054). HPV16 and/or HPV18 with other HR HPV type were detected in 31.0% (n=9) in LBCM and only 3.4% (n=1) in tissue biopsy samples (p=0.056). Only other HR HPV types were found in 6.9% (n=2) of LBCM and 10.3% (n=3) of tissue samples of tested women (p>0.05).

References

A lot of HR HPV types can colonize vagina and cervix, but often HPV16 or HPV18 alone or together penetrate in the tissue and cause cervical cancer.

00379

EVALUATION OF A CUSTOM CONFIGURED TECAN EVO FREEDOM WORKTABLE SET UP FOR PRE-ANALYTIC PROCESSING OF PRESERVCYT LBC SAMPLES FOR HIGH RISK HPV DNA TESTING IN PRIMARY SCREENING AND TRIAGE

08. HPV testing

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Background / Objectives

Pre-analytic processing of liquid-based cytology (LBC) samples is an important step preceding high risk (hr) HPV detection and should ensure adequate mixing of this per se inhomogeneous sample type. Automation of this process is desirable, particularly in the light of increasing demand expected with the introduction of primary HPV screening.

Results

A worktable set up of the TECAN EVO Freedom liquid handler was custom configured to automate the entire process of aliquot preparation from original Preservcyt LBC vials, including matching barcodes with secondary tubes, mixing and opening LBC vials, liquid transfer, closing LBC vials, identification and sorting of vials that are not suitable for further processing and process documentation. LBC vials sent in for hrHPV DNA testing (primary screening [P], N = 324; triage [T] N = 183) were anonymized and used for this evaluation. Matched pairs of manually and automatically preprocessed samples were tested in parallel with RealTime High Risk HPV (Abbott), a qualitative, clinically validated multiplex real-time PCR test for the detection of DNA from 14 hrHPV types, distinguishing HPV 16 and HPV 18 from non-HPV 16/18 hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), and detection of a human ß-globin ensuring sample adequacy. LBC vials were mixed manually for 15-20 seconds, while automated mixing was set for 15 seconds. The concordance of assay results obtained from matched pairs and corresponding kappa values were calculated. Average turn-around-time and hands-on-time of both pre-processing methods were estimated.

Conclusion

The TECAN processed 503/507 LBC vials. A total of 56 (17.4%) primary (P) and 167 (92.3%) triage (T) vials tested positive for hrHPV DNA after manual and automated aliquot preparation. Agreement of overall hrHPV results from matched pairs was 99.1% (k=0.97) for P-vials and 99.4% (k=0.96) for T-vials, while partial genotype pattern agreement was 99.1% (k=1.00) for P-vials and 98.9% (k=0.97) for T-vials, respectively. The TECAN aliquoted 48 LBC vials in 70 minutes without user intervention, while a minimum hands-on-time of 45 minutes was required for manual aliquot preparation.

References

The excellent agreement between hrHPV DNA test results from manually and automatically (TECAN Evo Freedom) aliquoted matched samples in conjunction with significant savings of labor time, full process documentation and a low rate of non-processed LBC vials demonstrates that the custom configured worktable configuration of the TECAN instrument evaluated in this study is well suited for improving the workflow of HPV testing LBC samples in high throughput settings.

00422

ATYPICAL GLANDULAR CELLS ON PAP TESTING AND ITS CORRELATIONS TO HPV

08. HPV testing

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Background / Objectives

The cytological diagnosis of atypical glandular cell (AGC) denotes cellular features beyond reactive changes that lack criteria for glandular neoplasia. ACG has a low incidence (0.2% of all cytologies) and as a result the diagnosis is challenging. Although a high percentage of reevaluation identify benign conditions, a significant subset of AGC cases also reflect significant lesions like endocervical adenocarcinoma and uterine or adnexal carcinoma. The prevalence of high risk HPV is 93% but a negative test does not exclude cervical pathology.
The aim of this study is to evaluate the prevalence, clinical findings, HPV correlation and follow-up of AGC results between 2008 and 2017 in a central Hospital.

Results

Pap smears classified as AGC between January 2008 and December 2017 were retrieved from an institutional cytopathological database. Clinicopathologic variables and follow-up were collected from medical records retrospectively.

Conclusion

A total of 84 cases were diagnosed in the 10 year time period. The mean age of the patients was 48.1 [22-83] years. The majority of women were multiparous and half of the sample (n=42) were combined contraceptive pill users. Only 12 patients were obese and 26 overweight; also, a small number (n=11) were smokers. HPV tests (COBAS test) were performed in 70 cases and the rate of high risk HPV was 61.4%. Other high risk HPV was the most common type (n=28), followed by HPV 16 (n=12) and HPV 18 (n=3). Positivity for p16/Ki-67 were found in 24 of all hrHPV cases. Colposcopy lesions were biopsied in 40 patients, 14 showed cervical intraepithelial

neoplasia (CIN) II/III and 15 low-grade lesions. A high number of these (n=27/29) tested positive for HPV and 20 were also p16/Ki-67 positive. 76 Seventy six transvaginal ultrasound were performed, four of them revealed benign endometrial pathology. Cervical sampling was collected in 50 cases; one of them was compatible with adenocarcinoma. Regarding treatment and follow up, 37 women were kept under surveillance, 7 were targeted for vaccination, 32 underwent cervix conization and 8 were submitted to hysterectomy, one in context of cervical adenocarcinoma. Only 3 women persist with AGC after 12 month follow up and there were no cases of further malignant pathology.

References

Despite published literature correlating AGC with high incidence of neoplasia, in our department this association was not confirmed. However HPV is increasingly associated with these cytological abnormalities. The results of our study, although limited by the small size of the sample, are in favour of a less agressive therapeutical approach at AGS diagnosis in Pap smears.

00463

PERFORMANCE OF THE SEMI-QUANTITATIVE HUMAN PAPILLOMAVIRUS GENOTYPING TEST ANYPLEX II HPV28 IN A REFERRAL POPULATION

08. HPV testing

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Background / Objectives

We compared by HPV type and viral load, the diagnostic performance of Anyplex II HPV28, a semi-quantitative DNA PCR (genotyping 14 high risk (hr)HPV types in set A and 5 hrHPV and 9 low risk (lr)HPV types in set B), to the gold standard HPV DNA test Hybrid Capture 2 (HC2) and to the mRNA test PreTect HPV-Proofer (`Proofer`), in detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+). We looked particularly at four specific groups of HPV types: 1) the five hrHPV types in Proofer, 2) the seven hrHPV types in the 9-valent HPV vaccine Gardasil9, 3) the HPV types in Anyplex II HPV28 set A, and 4) the HPV types in Anyplex II HPV28 set A and B, according to viral loads.

Results

In this cross sectional study, 296 women referred to follow-up with abnormal cervical cytology and/or persistent HPV infection, were included. The women had all three HPV tests performed from liquid based cytology samples.

Conclusion

The sensitivity of Anyplex II HPV28 to detect CIN2+ was 99% (95% CI 96-100) and specificity 43% (95% CI 34-53). Restricting to medium and high viral loads in Anyplex II HPV28 set A, sensitivity and specificity were 97% (95% CI 94-99) and 60% (95% CI 50-69) with positive (PPV) and negative predictive value (NPV) 75% and 93%, respectively, comparable to HC2. In a screening population, calculated PPV and NPV was 20% and 100%, respectively. Analyzing Anyplex II HPV28 by the five HPV types in Proofer (HPV16, 18, 31, 33, and 45), sensitivity and specificity were

comparable to Proofer`s according to CIN2+. Adding HPV52 and 58 raised sensitivity of CIN3+ to the level of Anyplex II HPV28 set A.

References

The clinical performance of medium and high viral loads in Anyplex II HPV28 set A was comparable to HC2, with additional benefit of genotype and viral load information useful in risk stratification. The detection of CIN2+ was not increased by adding set B of Anyplex II HPV28. Anyplex II HPV28 including all 28 HPV types is not suitable in primary cervical cancer screening.

00478

CO-TEST VALUE AFTER LOOP ELECTROSURGICAL EXCISION IN HIGH GRADE CERVICAL LESIONS

08. HPV testing

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Background / Objectives

Co-test (liquid-based cytology and HPV DNA testing) has been performed in the follow up of patients submitted to loop electrosurgical excision procedure (LEEP) for several years. The aim of this study was to evaluate the outcome of patients with high grade cervical lesions treated with LEEP, concerning middle follow up co-test results.

Results

We performed a retrospective 4-year analysis of patients who underwent LEEP with histological high grade cervical lesions (January 2012 to December 2015). Follow up was scheduled at 6-month intervals for 24 months after LEEP, and we reviewed the middle follow up co-test results. Cytology was considered as abnormal when the result was at least atypical squamous cells of undetermined significance (ASC-US). Patient outcomes were evaluated concerning the middle follow up co-test results.

Conclusion

124 patients were included, and co-test evaluation was performed between 9 and 20th months after LEEP (mean 13,8 months).

34 had a positive HPV DNA test – Group 1 (27,4%), with cytology abnormality in 12 of these patients (35,3%). The prevalence of mono-infection was higher than co-infection (79,4% vs. 20,6%). 32 patients test positive for high risk HPV (94,1%), and the most prevalent genotype was HPV-16 (32,4%).

The remaining 90 patients had a negative HPV DNA test (Group 2), 7 of which with cytology abnormalities in the co-test (7,7%).

Group 1 presented a superior mean age (41,5 vs. 36,9 years), and both groups had a similar percentage of Portuguese women (79,4% vs. 76,6%). Regarding positive LEEP margin status, Group 2 presented the lower percentage (15,9% vs. 34,2%).

At the 24th month of follow up Group 1 outcomes included: 2nd LEEP (n=3), hysterectomy (n=6), prolonged follow up (n=6) and return to screening program (n=17). For the same period of time, Group 2 outcomes included 73 returns to screening program and 1 prolonged follow up. 2 patients of Group 1 and 16 of Group 2 were lost during follow up.

References

In patients with high grade cervical lesions submitted to LEEP, positive HPV DNA co-test appears to be an important factor that can help predict less favourable, long term, outcomes.

00593

Pitfalls in HPV68a detection

08. HPV testing

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Background / Objectives

Despite the proved oncogenic potential, HPV68 genotype may be excluded from HPV screening tests and from newly developed vaccines due to its rarity in cervical cancer. HPV68 may exist in two subtypes (a and b), differing in 6% *E6*, 5% *E7* and 7% *L1* ORF sequence, and the HPV68a subtype is usually not detectable by primers targeting *L1* gene. The aim of the study was to evaluate the efficacy of routinely used cobas® 4800 HPV Test (targeting *L1* gene) in HPV68a detection.

Results

Cervical swabs (n=2198) obtained by physicians and self-sampled cervicovaginal swabs (n=217) were analyzed for the presence of HPV by cobas® 4800 HPV Test (cobas, Roche) and PapilloCheck® HPV-Screening test (PapilloCheck, Greiner Bio-One). For viral load assessment, HPV68 positive samples were further analyzed by a quantitative multiplex real-time PCR (qPCR) detecting of *E6* HPV68 gene and human *GAPDH* gene (internal control) using specific TaqMan® probes. Real-time PCR followed by high resolution melting (HRM) curve analysis and Sanger sequencing of *E6* PCR products was used for HPV68a/b subtyping.

Conclusion

HPV68 was detected in 39 of 2198 (1.77%) cervical swabs and 4 of 217 (1.84%) cervicovaginal swabs using PapilloCheck, with 33 single-type positive cases altogether. Cobas gave false negative result in 20 of 33 (60.6%) HPV68+ cases despite the median viral load of HPV68 was 1548 (1-320175) *E6*/ng DNA. The median viral load of HPV68 was 281 (9-17229) *E6*/ng DNA in true positive cases median viral load. HPV68a subtype was detected in all (20/20) false negative cases by HRM analysis as well as by Sanger sequencing. HPV68a subtype was detected in 3 of 13 (23.1%) and HPV68b in 8 of 13 (76.9%) of true positive cases, respectively.

References

Though cobas is routinely used HPV screening test, the false negative result was detected in 60.6% of HPV68 single-type infection cases due to its lower sensitivity for HPV68a. Prevalence of HPV68 genotype reported from the screening could be therefore underestimated. Due to low prevalence in cervical cancer, and given a substantial loss of specificity adding more HPV types in screening assays, HPV 68 may be excluded from newly developed screening tests or HPV vaccines. If the nonavalent vaccine successfully reduces the prevalence of its target genotypes, the prevalence of HPV68 may significantly increase. In this situation, the HPV genotyping assays not able to efficiently target both HPV68 subtypes will miss a clinically relevant proportion of cervical lesion in future.

00600

HPV INFECTION IN WOMEN AND MEN FROM INFERTILE COUPLES AND GAMETE DONORS

08. HPV testing

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Background / Objectives

Sexually transmitted infections (STI) are believed to cause fertility alternations. However, the exact impact of human papillomavirus (HPV) infection, the most prevalent STI, remains uncertain. The aim of the present study was to systematically investigate the prevalence of HPV infection in gamete donors and women and men from infertile couples and to find out if there is any relation to reproductive outcomes.

Results

Cervical swabs were prospectively collected from oocyte donors (OD, n=207) and women treated for infertility (IW, n=945). Semen samples and penile swabs were prospectively collected from sperm donors (SD, n=97) and men treated for infertility (IM, n=328). Cervical swabs and semen samples were tested for the presence of 14 hrHPV genotypes by cobas 4800 HPV system (Roche), then genotyped using PapilloCheck HPV-Screening system (Greiner Bio-One). Penile swabs were analysed by PapilloCheck HPV-Screening system only. The association between hrHPV positivity and fertility outcome or socio-behavioral and health characteristics was assessed using a statistical software R. All participants signed informed consent and filled in a questionnaire focused on their health status and sexual behaviour.

Conclusion

hrHPV prevalence was significantly higher in OD than in IW (28.0% vs. 16.1%, P<0.001). Interestingly, women who became pregnant spontaneously (19.6%) and women not treated with in vitro fertilization (IVF, 18.1%) were more frequently

hrHPV+ than women treated with IVF (12.7%, P=0.077). No associations between hrHPV+ of OD or IW and pregnancy or abortion rates were found. Overall, the hrHPV prevalence in penile swab or semen sample was 28.9% in SD compared to 35.1% in IM (P=0.312). Penile swabs were more frequently hrHPV+ than semen samples in both IM (32.3% vs. 11.9%, P<0.001) and SD (26.8% vs. 6.2%, P=0.006). IM with hrHPV+ semen sample had lower semen volume (median 2 ml vs. 3 ml, P=0.002), sperm concentration (median 13×10^6/ml vs. 26×10^6/ml, P=0.020) and total sperm count (median 33×10^6 vs. 71.8×10^6, P=0.004). No association between penile hrHPV positivity and semen parameters was found.

References

Despite high prevalence of hrHPV in both OD and IW, no associations between hrHPV positive status and pregnancy or abortion rates were found. IM were more frequently hrHPV positive than SD and the higher hrHPV positivity was found in semen samples compared to penile swabs. hrHPV positivity significantly influenced the sperm parameters in IM and could be therefore one of the cause of men infertility.

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00603

LUMINEX AND MULTIPLEX QPCR FOR DETECTING HPV GENOTYPES IN URINE SAMPLES.

08. HPV testing

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Background / Objectives

Norwegian girls have been invited to the HPV-vaccination program since 2009. As part of the national HPV-surveillance programme, urine samples from 17 and 21 years old girls have been collected before and at several timepoints after vaccination and used as a measure of HPV prevalence in the population. These data also provide a measure of the effect of the vaccine on the prevalence of HPV genotypes in the population.

Results

The original method for HPV genotyping in DNA from these urine samples was Luminex, where a mix of primers should amplify a region of L1 that can hybridize to specific oligos from 37 distinct HPV genotypes. The oligonucleotides are coupled to specific detectable beads, enabling multiplex detection of the HPV genotypes.

However, we question the performance of this method when vaccination results in a change in prevalence of HPV16 and/or HPV18, which may lead to variations in our ability to detect certain other genotypes. We therefore validate the performance of Luminex to detect specific genotypes in the presents or absents of HPV 16/18. We have also established an alternative multiplex qPCR assay, where a total of 14 HPV genotypes can be detected with specific Taqman probes against E6 or E7. We have combined detection of 4 targets in each reaction by choosing specific, compatible fluorescent probes.

References

We have compared the strengths and weaknesses of Luminex and multiplex qPCR for HPV detection from urine samples, and will share data illustrating the strengths and weaknesses of both methods.

09. HPV screening

00016

HPV SCREENING AMONG HIV–POSITIVE WOMEN IN ALBANIA

09. HPV screening

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Background / Objectives

Albanian National Statistics reflect a total of 312 HIV infected women. Naturally they face a much higher risk of HPV infection and cervical cancer than HIV uninfected ones, but there is no coverage of cervical cancer screening in the country at present. And as a consequence, there is a lack of data on the association between cervical cancer and HIV. The aim of this study was to determine the prevalence of HPV infection of high- and low-risk types and to analyze how HPV infection manifests itself in HIV-infected women in Albania.

Results

A number of 105 HIV positive women aged from 30 to 65 years, who attended the Outpatient Clinic of Infectious Diseases Unit of Mother Theresa Hospital Center, responded in the year 2017 to the invitation for a routine HPV cervical infection screening. Sampling was done by self-collection using digene Female Swab Specimen Collection Kit (Qiagen, Gaithersburg, MD). Samples were analyzed with Hybrid Capture 2 (HC2) Assay (Qiagen, Gaithersburg, MD). Demographic, epidemiological, and behavioral data were obtained from all responders through a standardized questionnaire.

Conclusion

At the time of HPV screening: 91% (96/105) of women were on antiretroviral therapy and 31.4% (33/105) of them were on AIDS stage (A3, B3 and C1- C3). The median CD4+ T-cell count was 400 cell/mm3. Only 8 women (7.6%) have undergone, once in their lifetime, a cytological screening for cervical cancer, and this with normal results. 65% of women presented a “not detected”(ND) or low viral load. The overall prevalence of HPV cervical infection in HIV-positive women in Albania was 44.7%. Oncogenic hr-HPV was detected in 41.9% (44/105) of them, whereas 22.85% (24/105) were infected with lr-HPV. In a percentage of 16% multiple infections with hr-HPV and lr-HPV types, were detected. From these, the majority (71.4%) were

found in women of ≥ 41 years. Lower CD4 counts (<200 cell/mm3) were associated with 40% of hr-HPV positivity, and were not associated with marital status, no. of lifetime or recent partners, no. of pregnancies, use of contraceptives.

References

For Albania, a country with low endemic rates of cervical cancer, a high HPV DNA infection prevalence signalizes an increased risk of cervical cancer among HIV-positive women. Therefore it is of a great importance to actively screen HIV infected women for cervical infection with the objective of finding differences with regard to persistence of high risk HPV infection or progression of CIN among highly active antiretroviral therapy (HAART) treated versus non treated women in Albania.

00019

URINE DETECTION OF HPV ONCOPROTEIN: IS IT A NEW ALTERNATIVE FOR CERVICAL CANCER SCREENING?

09. HPV screening

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Background / Objectives

Background: Cervical cancer (CxCa) is a significant public health problem, especially in low- and middle-income countries, where women have little access to CxCa screening; consequently, 80% of CxCa related mortality occurs in these regions. The development of screening methods that need less infrastructure thus represents an urgent medical need.

Objectives: To evaluate the detection of HPV16 and HPV18 E6 oncoprotein in urine samples from women attending at Barretos Cancer Hospital.

Results

Methods: Between January 2017 and September 2017, 124 women, aged 25 to 64 years, who attended at the Prevention or Gynecologic Oncology Departments of Barretos Cancer Hospital (HCB), Barretos, Sao Paulo, Brazil were recruited. At study enrollment, each woman provided urine and self-collected vaginal samples; then the physician collected a cervical sample. Urine-based protocols to measure HPV-DNA via Cobas® HPV Platform (Roche, CA, USA) and E6 oncoprotein levels using the

OncoE6™ Cervical Test (“E6 test”; Arbor Vita Corp., CA, USA) were developed and applied.

Conclusion

Results: The median age of participants was 40 years. Cervical disease status was categorized as positive (CIN2+) in 63.7% of women. Of those, 44/79 (55.7%) had a histological diagnosis of invasive carcinoma, 26/79 (32.9%) of CIN3 and 9/79 (11.4%) of CIN2. High-risk (HR) HPV-DNA test was positive in 66% of the physician and 65% of the vaginal self-collected samples and 50.0% of the urine samples. HPV16 was the most frequent type detected (51.2%) of the physician collected samples. The HPV16/18-E6 test was positive in 31% of the physician-collected samples, 20% of the vaginal self-collected and 21% of the urine samples. Considering only HPV16 or HPV18 positive samples on Cobas test, the HPV16/18-E6 detection rate was 73.1% (38/52) for the physician sampling, 50% (25/50) for the self-collected vaginal sample and 53.5% (23/43) for the urine specimens. The sensitivity and specificity for CIN2+ detection using urine was: 30%% and 95%, respectively for HPV16/18-E6 test and 72% and 89%, respectively for HPV-DNA test.

References

Conclusions: Our results suggest that using urine could be an acceptable option to perform HPV16/18-E6 test since the HPV16/18-E6 test positivity rates for self-collected vaginal sample and urine were similar. However, the urine-based E6 test needs further protocol development and standardization.

00120

NON-16/18 HPV GENOTYPES PREDOMINANT IN BIOPSY SAMPLES WITH HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS IN WOMEN WITH PRECEDING NEGATIVE HPV TESTS

09. HPV screening

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Background / Objectives

High-risk human papillomavirus (hrHPV) testing has been increasingly used in clinical practice in recent years for triaging equivocal cytology or co-testing with cytology. Recent studies indicated that a considerable portion of patients with high grade cervical lesions (≥HSIL) had preceding negative hrHPV tests. The study attempted to elucidate the factors potentially contributing to the finding by testing biopsy samples from these patients.

Results

We retrospectively reviewed the correlation of cytology, histology and hrHPV testing from our Cytology Laboratory database of 130,648 Papanicolaou (Pap) tests between March 1, 2013 and June 30, 2014. Patients with negative hrHPV tests and ≥HSIL on follow-up biopsy were identified, and the corresponding paraffin blocks were tested for HPV on Cobas system, DNA microarray against 40 HPV genotypes, and DNA sequencing.

Conclusion

Twenty-one (8.3%) of 252 women with ≥HSIL on biopsies had preceding negative HPV tests. A wide range of HPV genotypes were detected in 20 of the 21 (95%) biopsy samples, including non-16/18 hrHPV (50%), non-hrHPV (30%), and HPV16/18 (20%). HPV59 and 45 were most commonly detected HPV genotypes (50% and 29%, respectively). One sample was negative for all three tests (1/21, 5%).

References

HPV was detected in vast majority (95%) of the biopsy samples with HSIL in women who had preceding negative HPV tests, including hrHPV (70%) and non-hrHPV (30%). In addition to those infected by non-hrHPV genotypes or possible non-HPV related dysplasia (5%), multiple factors might have contributed to the prior false-negative HPV tests, including inadequate sampling, interference material, technical errors, and reduced L1 gene expression in high-grade lesions. We noticed that non-16/18 hrHPV genotypes were most commonly detected in the cohort with HPV59 and HPV45 predominance, a genotypic prevalence pattern markedly different from that in general population in US. This may suggest these genotypes are relatively less sensitive on Cobas test or have lower expression level of L1 gene. Additional studies will help to validate the findings and elucidate the contributing factors and underline mechanisms.

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00135

Distribution of genotypes in a mRNA HPV-positive screening population

09. HPV screening

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Background / Objectives

In Sweden, updated recommendations for cervical cancer screening was released in 2015 (1). In the new program, women between 30-64 years, is screened primary with HPV followed by cytology on positive samples. In Örebro county, the new program was introduced in 2016 and for HPV screening, a test detecting mRNA in 14 hrHPV genotypes is used. This test is however not providing genotype information. The aim of this study was to investigate the distribution of genotypes in a HPV-positive screening population in Örebro, Sweden.

Results

HPV positive samples (HPV Aptima, Hologic) between November 2016 and April 2017 (n=530) were included in the study. Genotyping was performed at the same sample as the screening test by extracting DNA directly from residual material in the Aptima specimen transfer tube and genotype using Anyplex II (Seegene).

Conclusion

More then half of the study population were in the age group 30-39 years (n=274, 52%), 32% were 40-49 years (n=173) and 16% 50-58 years (n=83). Despite of a positive screening result, 46 samples tested negative in the genotyping (9%). The most common genotypes were HPV31 (n=93), HPV16 (n=76), HPV52 (n=57) and HPV68 (n=49) and of 28 detectable genotypes, 27 was present in at least one sample. Single infections (n=281) were more common than multiple infections (n=203) and the distribution was similar between the three age groups (Fisher´s Exact Test, p=0.867).

References

A wide repertoire of HPV genotypes was present without differences between age groups. Also, a distinctive portion of mRNA positive samples were found to be negative when DNA tested. Negative samples will be further evaluated with a second HPV test, using different viral target genes.

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00144

Countries of Eastern Europe and Central Asia: the situation of HPV infection in HIV-positive women

09. HPV screening

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Background / Objectives

The frequency of detection of HPV varies greatly depending on the region of residence of the woman. Also HIV-infected women have a higher risk of HPV infection than HIV-negative women, and a higher risk of persistence and malignancy.

The aim of the study was: to study the prevalence of human papillomavirus of high carcinogenic risk (HPV HCR) in HIV-infected women in some countries of Eastern Europe and Central Asia.

Results

647 HIV-infected women from Russia, Belorussia, Armenia, Azerbaijan, Tajikistan and Kyrgyzstan were examined from September 2017 to December 2017 . All women underwent HPV-test with the determination of 14 types of HPV HCR (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).

Conclusion

Among the 647 women surveyed, mostly young people (under 40 y-s) predominated. As a result of the HPV-test, 265 (41%) of HIV-infected women were diagnosed with HPV HCR. The percentage of HPV detection ranged from 28 to 48%: Armenia - 39%, Azerbaijan - 43%, Belarus - 28%, Kyrgyzstan - 46.5%, Tajikistan - 37.8%, Russia (Samara) - 48%. All 14 HPV HCR genotypes were diagnosed in HIV-positive women in the region.

The distribution of HPV genotypes is different for these countries: 16 and 68 HPV genotypes are registered in Armenia (33.3% and 23%, respectively), in Azerbaijan 16, 18 and 56 HPV genotypes (32.6%, 20.9%, 20.9%), in the Republic of Belarus - 16 (28.6%) and 56 (28.6%), in the Republic of Kirghizia - 16, 31 and 68 (23.9%,

21.7% and 21.7% respectively), in Tajikistan - 16.31, 56 (29.7%, 21.6% , 21.6%), in Samara (Russian Federation) - 52 and 16 (23.6% and 22.2%).

HPV infection was caused by a combination of several genotypes in 49,1%/. The leading genotypes amond 265 HIV-infected women with HPV were: 16 genotype - 26.4%, 31 genotype - 13.6% and 18 genotype - 9.4%.

References

There is a high incidence of HPV infection in HIV-infected women.

References

Given the high risk of developing cervical cancer and the wide spectrum of detectable genotypes of HPV HCR in this group, it is necessary to use a test system to diagnose the 14 genotypes of HPV. The results should be taken into account when planning vaccination in the region.

00190

INCIDENCE OF HUMAN PAPILOVIRUS INFECTION IN RIVERSIDE WOMEN OF AFLUENTES AMAZONAS RIVER - BRAZIL

09. HPV screening

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Background / Objectives

Introduction: The relationship between cervical intraepithelial lesions and malignant potential associated with human papillomavirus (HPV) infection is already well established. The identification of HR_HPV types is very important to the prevention of this neoplasm and in evaluating the vaccine efficacy. Low-income populations with low socioeconomic status, especially in developing countries, are the most disadvantaged due to get access to public policies for prevention and diagnosis, viral dynamics and the evolution of neoplasia, as is the case with river populations in Rio Amazonas.Objective: This study aims to identify the presence of HPV-DNA in cervical intraepithelial lesion of riverside women from the tributary communities of the Amazon River.

Results

Method: A total of 123 cervical samples were collected in BLM (Cellpreserv) from riverside Negro and Madeira rivers. The cytopathological material was automatically processed in the KLP 2000 (Kolplast) and classified according to the Bethesda System (2011). The residual material was submitted to DNA-HPV genotyping by the MicroArray methodology (Euroimmun). The tests were performed in duplicate, using a positive and negative HPV control. This project has been approved by the Ethics Committee of the Santo Amaro University - SP (Brazilian Plataform - CAAE: 61414216.4.0000.0081).

Conclusion

Results: 123 cell samples submitted to cytology analyze, 12 (9.7%) samples presented cervical intraepithelial lesions, 2 (1.6%) samples were classified by ASCUS, 5 (4.1%) samples were diagnosed as LSIL, 5 (4.1%) samples classified as

HSIL. 4 (3.2%) samples presented cervical lesion had HPV infection. 2 (1.6%) samples were from the Negro River, and 1 (0.8%) sample presented a cytologic picture as LSIL and had HPV 43,53,72 types. 1 (0.8%) sample showed a cytologic picture as HSIL, and HPV 51 and 39 infection. 2 (1.6%) samples were from the region of the Madeira River. 1 (0.8%) sample showed a cytologic picture of LSIL and 1 (0.8%) sample was classified as HSIL, both sohwed HPV 61 infection. The women from the Negro and Madeira Rivers regions exhibited 56% and 66.7% of HR_HPV infections, respectively, and 43.75% and 33.33% of LR_HPV infection in the Negro and Madeira Rivers, respectively. 25 (20.3%) samples with cytologically diagnosed as reactive status had HPV infection. The most prevalent types were HPV 16 (20%) and 45 (16%). 2 (1.6%) samples classified as normal status had HPV 16 (50%) infection.

References

Conclusion: The study leads us to consider that according to the relationship between the social, behavioral factors in the cytological and molecular study of the population of riverside women in the of the Amazon River have a high risk to develop cervical cancers associated a HSIL and HR_HPV types found in both regions.

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00225

Organization of in-depth examination for diagnostic cervical cancer of Rostov region female population

09. HPV screening

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Background / Objectives

Cervical cancer in Russian Federation ranks as the 5th most frequent cancer among women and the 2nd most frequent cancer among women between 15 and 44

years of age. Liquid-based cytology with partial automation in which a glass slide is pre-read by the robot improves the accuracy of cytological examination and results in fewer unsatisfactory smears. The HPV test is needed to triage of indeterminate Cytology results, which accounted for around half of abnormal results. The efficiency of these methods demonstrated in a programme of organized screening.

Objective: to evaluate co-testing in the opportunistic screening for cervical cancer

Results

Since 2014, in Rostov-on-Don and the Rostov region a regional program of cytological cervical cancer screening with parallel HPV testing has been implemented. Liquid-based cytology BD TriPath and clinically validated test COBAS RealTime High Risk HPV that provides qualitative detection of 14 high risk HPV types, three results per test reported corresponding to HPV 16, HPV 18, and 12 other high risk HPV, single and mixed infections) are used for screening purposes in the specialized laboratory of the Regional Consultative and Diagnostic Center. The performance of all tests is automated

Conclusion

As a result of 4 years work, on the basis of Rostov Region Regional Counseling and Diagnostic Centre, an algorithm for screening and in-depth diagnostics of cervical pathology has been developed. This algorithm is optimal for the region in the absence of a national cervical screening programs.

During the period of 2014-2017 cytology is conducted for 267 510 women. HPV testing is conducted for 65 993 females. Pathological changes in the epithelium identified by cytology are detected in 45 477 women (17%): LSIL – 43 131 (95,7%), ASC-US/ASC-H - 819 (1,8%), HSIL – 909 (2%), the cancer is detected in 213 women (0,5%). Positive results in HPV testing contribute to 9551 (21%).

References

Complex approach to the diagnosis of cervical lesions and coordinated working process of medical institutions can significantly shorten the patients examination process and help to timely use high-tech testing and treatment methods in frames of one multi-disciplinary diagnostic center.

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00385

High prevalence and concordance of anal and cervical HPV genotype detection

09. HPV screening

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Background / Objectives

The same high-risk (HR) Human Papilloma Virus (HPV) types associated with cervical cancer can also cause anal cancer and its precursors (AIN)[1]. The incidence of anal cancer is increasing by 2% each year in women and men[2]. Women with history of CIN have a 10 fold increased risk of anal dysplasia. Aim was to explore the correlation between cervical and anal HPV infection as well as the development of cervical and anal dysplasia.

Results

Women with gynecological clinical indication (HPV/cytology/histology) were recruited. Initially, anal cells were collected using swabs (PAPCone) for HPV testing and cytological examination followed by a cervical smear (Cervex-brush and Cytobrush) to prevent contamination between the smears taken. All women with an anal HR-HPV positive finding were followed up. Anal HR-HPV positive women underwent rectal examination and standard anoscopy. Anal and cervical smear test are repeated after 12 months to document possible changes or clearance in HPV genotypes. The anal HR-HPV positive women are followed up for 48 months.

Conclusion

This interim analysis includes 66 women. Cervical examination demonstrated CIN I (9), CIN II (14), CIN III (8), in addition, VIN I (1), VIN II (1), VAIN I (1), VAIN II (1), VAIN III (2), metaplasia (2) and condylomas (1) were found. In six cases, the histology showed no abnormality. 53 women (80.3%) had ≥1 anal HPV type (3 anal smears unsatisfactory DNA amount) and HR-HPV was found in 48 women (72.7%). From these 46 (95.8%) were also positive at the cervix, 41 (85.4%) women had at

least one identical cervical HPV type. The anal smear tests showed no clinical indication. 26 women underwent rectal examination and anoscopy. In 25 cases, no AIN was diagnosed and one case had a non-valid result. Findings were healed fissures (2), hemorrhoids (6), condylomas (1), colon irritable (1) and a fibroid (1). Fourteen anoscopies demonstrated no findings. Nine women attended the 12-month follow up so far. Six underwent surgical intervention at the cervix in the past year. In 4/6 cases, cervical and anal HPV type changes after surgery were observed. In 2/6 cases, the surgical removal of one particular cervical HPV type also lead to the clearance of the identical HPV type in the anal smear test.

References

HPV infection in the anus in women with cervical clinical indication is common. The concordance between cervical and anal HPV is prominent (69.7%). Despite this very high anal infection rate, the rate of anal dysplasia is low as compared to cervical sites. Recruitment is ongoing.

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00400

NEW MOLECULAR MARKERS IN HPV INFECTION RISK STRATIFICATION: SYSTEMATIC REVIEW

09. HPV screening

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Background / Objectives

Cervical cancer is one of the most common oncologic diseases in women worldwide, with its highest mortality rates in countries without a well established mass screening program, which is why we can safely say that screening is critical in reducing morbidity and mortality from this cancer. It is also well established that human papillomavirus (HPV) infection is associated with cervical cancer, however, since most lesions caused by HPV regress and only some progress to cancer, new biological markers able to identify clinically relevant HPV infection and avoid needless colposcopy referral are still needed, and that is the aim of this review.

Results

A search was conducted using the Pubmed database, restricted from 2008 onwards, using the keyword “papillomaviridae” in combination with “RNA, messenger” or “E6/E7”, “p16” and “ki-67”, “methylation”, “microRNAs”, “BIRC5”, and “DNA Topoisomerases, Type II” or “MCM2, and the Web of Science Core Collection, restricted to the same time frame, using the keywords “HPV” and “cervical cancer” in combination with “mRNA” or “E6/E7”, “p16” and “ki-67”, “methylation”, “microRNA” or “miRNA”, “BIRC5”, and “TOP2A” or
“MCM2”. Reference lists of relevant articles were also included. Preference was given to experimental and observational studies with comparison groups.

References

E6/E7 mRNA and p16/ki67 dual-stained cytology are the most studied new molecular biomarkers, with evidence in regards to the benefit they would provide to screening, particularly as a triage test before referral to colposcopy, however, more robust studies and a cost benefit analysis are still needed if they are to be included in mass screening protocols. Assessment of methylation levels also appears to be an interesting way to identify clinically relevant HPV infection, once agreement pertaining to the genes associated with the highest diagnostic accuracy is achieved.

Lastly, microRNAs, BIRC5, TOP2A and MCM2 are novel targets that also show great promise and should be the focus of future studies.

00442

ACCEPTABILITY OF POINT OF CARE HPV-BASED CERVICAL SCREENING: A QUALITATIVE SYSTEMATIC REVIEW

09. HPV screening

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Background / Objectives

The World Health Organization (WHO) recently recommended high risk HPV (hrHPV) testing for primary cervical screening in all countries, including low- and middle-income settings. HPV testing has high sensitivity and specificity compared to conventional cervical cytology, allows for less frequent screening, and when used at the point-of-care (POC), bypasses the need for sophisticated laboratories. Testing for hrHPV at POC means that results can be provided in a shorter timeframe (60 minutes compared to up to 2 weeks for Pap smears in high-income settings and much longer in other settings) allowing for quicker turnaround of results, faster access to treatment, a reduction in patient loss to follow-up and, in time, reduced morbidity and mortality. Such new technologies can however place additional stress on women, health care workers (HCW) and clinic workflow. It is critical to better understand the impact on different end-users to develop better communication messages that will make this user-friendly technology more acceptable. This qualitative systematic review will explore women's and health care providers' experiences and perceptions of cervical cancer screening and the socio-cultural factors influencing the acceptability of HPV-based cervical screening in all settings.

Results

The review will be conducted in accordance with the PRISMA guidelines. Two independent reviewers will screen all titles and abstracts to confirm the relevance of the studies according to the inclusion criteria of qualitative studies that explore acceptability of HPV-based cervical screening, from the perspective of women ('patients') and healthcare providers in any setting. Data extracted will include title, authors, country, study design, research aim, intervention, data collection method, theory used, outcomes and results. Studies will be analysed using the meta-aggregation approach. The quality of the included studies will be assessed using the

Critical Appraisal Skills Programme tool. Findings from the review will be available for presentation at the conference.

References

With advancements in cervical screening methods being rolled out around the world, it is critical to explore how these technologies are understood by women and their health care providers across settings. Qualitative research is important to provide contextual information about how to prepare women and health facilities for HPV-based testing. The findings of this qualitative systematic review will provide guidance for action and inform future health education programs and interventions to increase uptake of HPV-based cervical screening globally.

00530

EVALUATION OF THE EFFICACY OF THE TREATMENT OF VAGINAL INTRAEPITHELIAL NEOPLASIA IN PUBLIC HOSPITAL IN SAO PAULO, BRAZIL

09. HPV screening

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Background / Objectives

Vaginal intraepithelial neoplasia (NIVA) is a premalignant lesion marked by the presence of squamous cells with atypia and no invasion. It has an incidence of 0.3 per 100,000 women in the United States and corresponds to 0.4-0.5% of intraepithelial lesions of the lower genital tract (1, 2). and high grade categories (2 and 3): NIVA 1 involves the lower third of the epithelium, NIVA 2 and 3 more than two-thirds to the total thickness. NIVA of high grade precursor of the carcinoma of the vagina, in analogy to the Cervical Intraepithelial neoplasia (NIC).The aim of study was the clinical evaluation of NIVA treatment and therapeutic measures, comparing the treatment of the laser with the immunological treatment and the rates of relapse in both treatments.

Results

Series of cases sent to the Clinical Hospital of the University of São Paulo with biopsy diagnosed with NIVA, through electronic medical record research. Evaluation of the type of treatment: laser, imiquimode or both and the result, regression, corresponds to a normal colposcopy or biopsy or biopsy with the functions of less than or equal to a NIVA 1; persistence, corresponds to patients who are submitted to biopsy treatment with NIVA 2 or 3; or evolution to carcinoma. In addition, the patients with regression and continued in follow-up, evaluating the occurrence of relapse. Statistical analysis was performed as Student's test for continuous variables and chi-square test for categorical variables. The tests were performed in the Numbers® Version 5.0.1 for Mac OS program.

Conclusion

148 patients had NIVA diagnostic, 59 had NIVA 1, and an expectant management was performed. The remaining 89 patients were diagnosed with high grade NIVA (2 or 3). Thus, 56 patients with high-grade NIVA evaluated in this study, 76.8% underwent laser / megapulse treatment ; 21.4% to imiquimode and 1.8% to imiquimode + laser. Of the 43 patients submitted to laser, 58.1% presented improvement, 30.2% persistence, 4.7% progressed to carcinoma and 7 are still in follow-up, with no results yet after treatment and 5 presented relapse. Of the patients submitted to imiquimode, 66.7% presented improvement and 33.3% presented persistence of the lesion. And of the 8 patients with improvement, 3 presented recurrence. When comparing the recurrence rate of each treatment, both laser and imiquimod treatment had a 25% relapse after regression in the initial total - 5 cases of 25 with regression after laser and 2 cases of 8 with regression with imiquimode.

References

Imiquimode presents as a possible alternative treatment for high-grade NIVA. However, further studies are needed to complete the treatment of HPV, with the objective of returning to the lesions and clarifying the HPV, in order to reduce relapses, to follow a minimum number of patients evaluated.

00608

HPV INFECTION AMONG HIV-POSITIVE MEN: A FIVE-YEAR REVISED EXPERIENCE OF A DIAGNOSIS LABORATORY.

09. HPV screening

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Background / Objectives

The spread of HIV epidemics globally has increasingly drawn attention to the interaction between HIV and the “classic” sexually transmitted infections (STIs). A consensus has grown that other STIs increase the spread of HIV, following on from the early epidemiologic studies that explored the epidemiologic synergy between STIs and HIV. However, the interaction of the many STIs with HIV is potentially complex, with the possibility of reciprocal influences on susceptibility, infectiousness, and the natural history of infections. There is growing evidence of a significant burden of human papillomavirus (HPV) infection and associated disease in men. HIV infection increases HPV prevalence, incidence, and persistence and is strongly associated with the development of anogenital warts as well as anal, penile, head and neck cancers in men. Despite increasing access to antiretroviral therapy, there appears to be little benefit in preventing the development of these cancers in HIV-positive men, making prevention of infection by vaccination and information, a priority.

The authors present 5 years revised casuistic as a reference laboratory center in sexually transmitted infectious diseases diagnosis.

Results

Male samples were tested by HPV-molecular and conventional-cytology methods. HPV molecular methods used where: Hybrid Capture 2 (hc2, Digene); Clart human papillomavirus 2 (Genomica) and PapilloCheck. The cytological results were registered with comprehensive classification system, multi-axial nomenclature SNOMED. The diagnosis of “classic” sexually transmitted infections (STIs) as Herpes Simplex virus 1 and 2, Syphilis, Gonorrhea, Chlamydia trachomatis, Ureaplasma and Mycoplasma infections statistics were used for data analysis; the Fisher exact test was employed to assess the association between categorical variables. P-values (2-sided test) less than 0.05 were considered significant.

Conclusion

The results obtained for the incidence of most frequent HPV genotypes in men and MSM are in agreement with several studies [Dunne EF, 2006]. The most common anogenital HPV types detected in men varied by study but were similar to the types commonly detected in women.

Type 16 was consistently found among the most common; however, other types were also reported (types 6, 11, 18, 31, 33, 42, 52, 53, 54, 59, and 84) [Dunne EF, 2006], but a shift possibility can occur with universalization of the vaccine.

References

This study will contribute to a better understanding of the wide spectrum of male HPV infection.

On genotyping tests multiple infections decreased by the severity of the cytological interpretation, revealing that persistent and relapsing HPV infections are at higher risk for anal dysplasia development and malignant transformation. HPV infection appears to occur early in MSM.

10. Self-sampling

00003

PREVALENCE OF HUMAN PAPILLOMAVIRUS ON THE HANDS OF HEALTH PROFESSIONALS

10. Self-sampling

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Background / Objectives

The HPV infection can lead to a variety of lesions both benign and malign. [1] The main route of transmission is sexual intercourse but there is evidence that supports other routes such as self and heteroinoculation through the hands. [2-9] The objective of this work was to determine the HPV prevalence on the hands of health professionals – doctors, nurses and medical auxiliaries.

Results

Health profissionals from four specialties – dermatology (DERMA), otolaryngology (ORL), gastroenterology (GASTRO) and obstetrics&gynecology (GINECO) – working in Hospital de Santa Maria in Lisbon, participated voluntarily in the study by signing an informed consent, completing a questionnaire and allowing the sampling of their dominant hand (through the use of the kit “LINEAR ARRAY HPV Genotyping Test”®, a spiral brush and a scraping with a scalpel blade) to search for DNA of different HPV genotypes: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84(MM8), IS39 and CP6108.

Conclusion

There were 102 participants in the study and the distribution by specialty was: DERMA - 26; ORL - 25; GASTRO - 19; GINECO - 32. Among the total were 32 doctors (31.37%), 44 nurses (43.14%) and 26 medical auxiliaries (25.49%). The mean age was 40.2 years. Regarding sexual orientation: 100 heterosexual participants and 2 men who have sex with men. On average, the studied population had 1.02 sexual partners in the last 6 months.
In total, 37 of the 102 study participants were positive for HPV on the hands. The most frequently found genotype was 6 (n = 14), followed by 51 (n = 11) and 66 (n = 10). The

distribution of positive specimens by specialty and their respective genotypes is shown in the table:

Specialty	Total of participants	Total HPV+ samples (%)	Detected genotypes (n)	High-risk	Low-risk
DERMA	26	8 (30.77)	6 (3), 51 (3), 66 (2)	51, 66	6
ORL	25	10 (40)	6 (3), 11, 51 (4), 66 (2)	51, 66	6,11
GASTRO	19	8 (42.11)	6 (2), 11, 51 (3), 51+66, 66	51, 66	6, 11
GINECO	32	11 (34.38)	6 (6), 56+66, 16+83, 66 (3)	16, 56, 66	6, 83
Total	102	37 (36.27)	6 (14), 11 (2), 51 (10), 66 (8), 16+83, 51+66, 56+66	16, 51, 56, 66	6, 11, 83

References

In the present study, a high prevalence of health professionals with positive samples for HPV on the hands was observed - 36.27%. In 56.76% of these samples high-risk HPV subtypes were identified making appropriate the discussion about the risk of virus transmission to patients and devices which will later be used in patients.

We thank Professor Eduardo Franco for the contribution to the accomplishment of this work.

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00290

WILL HPV SELF-SAMPLING DIMINISH THE SOCIAL INEQUALITIES IN THE FLEMISH CERVICAL CANCER SCREENING PROGRAM?

10. Self-sampling

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Background / Objectives

This study aimed to study the social inequalities in the uptake of cervical cancer screening, when self-sampling kits were offered to Flemish non-attenders of the Flemish cervical screening program.

Results

The study was based on data that were obtained from a randomized controlled trial (n=16,660) measuring how offering HPV self-sampling affected screening participation. Women either received a kit to perform a self-sample for HPV testing or a letter offering the opportunity to order a kit. Socioeconomic data on the study population were derived by linkage to the Crossroads Bank for Social Security, using the National Social Security Number. Descriptive analyses were conducted to assess the distribution of socio- demographic (current and nationality of birth) and SES

variables (work intensity at household level and preferential tariff as a proxy for poverty).

Conclusion

Women with a preferential tariff, have a significant higher risk of not returning a self-sampler (OR: 1.66 (95% CI: 1.47-1.86). There was a positive association between work intensity at household level and participation. Women living in (quasi-)jobless households, were more likely not to participate (OR: 1.36 (95% CI: 1.21; 1.54) than those not living in a jobless household. Participation in the study was 18.1% for women who had Belgium as their nationality at birth and 20.2% who have Belgium as their present nationality. Participation in the study was 10.8 % for women born in Eastern Europe and 4.8% for women born in Maghreb or Turkey. The crude OR for not being screening with a self-sample, for having a nationality at birth other than Belgium or being from the Netherlands was 2.36 (95% CI: 2.13- 2.62). The OR for not participating for having a present nationality other than Belgium or being from the Netherlands was 1.86 (95% CI: 1.63- 2.11).

References

Here we show that low SES, as measured by preferential income and household work intensity, was strongly associated with low participation in being screening with self-sampling, and that immigrants were less likely to participate. Our results demonstrate that cervical screening with a self-sampling kit does not socially balance cervical cancer screening. Social inequalities in the uptake of cervical cancer screening, when self-sampling kits are offered to Flemish non-attenders, remained and other routes need to be explored.

The research was funded by the Flemish government.

00342

Performance of 6 methylation markers tested on self-collected dry samples – feasibility study

10. Self-sampling

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Background / Objectives

In high-income countries, a high proportion of cervical cancers are diagnosed in screening non-attendees. One approach to improve screening coverage is to offer vaginal self-sampling for HPV testing. To improve the rather low specificity of HPV testing additional markers such as HPV-specific DNA methylation can be used.
Aim of this feasibility study is to determine the performance of the methylation marker assay GynTect®, comprising 6 methylation markers, on dry self-collected samples of different storage age.

Results

100 samples collected during an earlier study 2013/14 were stored in PreservCyt at room temperature. Furthermore, we aim to collect up to 100 fresh self-samples among patients from ourcolposcopy clinic. For the fresh samples, the Evalyn Brushes are stored at room temperature after self-sampling and after one week, cells are transferred to ThinPrep PreservCyt solution for analyses. GynTect® and HPV-testing (Abbott RealTime HighRisk HPV Test) were performed on both, old and fresh samples.

Conclusion

Preliminary data show a good performance of GynTect® on fresh samples, whereas older (>4 years) samples seem to have insufficient DNA quality to reliably determine the methylation status of the samples.

References

This feasibility study has just started and only few preliminary data is available up to now. At Eurogin, we will have data for the methylation assay on about 100 older and 100 fresh samples and both, HPV assay and the methylation assay, can be

evaluated regarding the performance, reproducibility and general handling on self-collected dry cervical samples.

00372

EVALUATION OF THE INNO-LiPA HPV GENOTYPING EXTRA II ON UCM PRESERVED FIRST-VOID URINE

10. Self-sampling

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Background / Objectives

Self-sampling opens opportunities to increase the participation rates in screening programs and may improve today's cervical cancer prevention. Non-invasive urine collection is considered the preferred way of self-sampling compared to vaginal/cervical swabs.

The INNO-LiPA HPV Genotyping Extra II allows identification of 32 HPV genotypes and excellent performance has been shown using cervical scrapes. Our study aim was to develop a protocol for first-void urine and to demonstrate equivalent performance of the INNO-LiPA HPV Genotyping Extra II in comparison to cervical samples.

Results

Samples: UCM-preserved first-void urine samples collected between 2010-2012 and stored at -20°C until analysis. HPV DNA results for genotype 16 and 18 were available based on real-time PCR data on urine and cervical samples.

INNO-LiPA HPV Genotyping Extra II testing: DNA was extracted using the QIAamp DNA mini kit with a starting volume of 200 µL and a final elution volume of 50 µL. Amplification and LiPA hybridization was performed according to the manufacturer's instructions.

Conclusion

The INNO-LiPA HPV Genotyping Extra II showed HPV DNA positive results on all samples with a historical positive reference result on first-void urine. In comparison to

the reference data which used 4 mL UCM-preserved urine and included a concentration step, these data indicate that it is possible to test directly on a reduced amount of first-void urine.

Concordant HPV genotyping results for HPV 16 and 18 were obtained on first-void urine in comparison to the HPV genotyping result on the corresponding cervical sample (collected on the same day or another day) in more than 90% of the samples tested. Additional HPV genotypes were identified using the INNO-LIPA HPV Genotyping Extra II.

References

A testing protocol was developed for the INNO-LiPA HPV Genotyping Extra II enabling the use of self-collected first-void urine as input sample. The high analytical sensitivity of the SPF10 Plus-based amplification allowed the use of a limited amount of sample volume. A good concordance between HPV genotyping results in urine and cervical scrapes were obtained. Further investigation by direct comparison of first-void urine and cervical scrapes with the INNO-LiPA HPV Genotyping Extra II is ongoing.

00383

USABILITY OF THE COLLI-PEE: A FIRST-VOID URINE SELF-SAMPLING DEVICE

10. Self-sampling

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Background / Objectives

The aim of this study was to compare the usability of the previous version (CP2000) of the Colli-Pee to the current improved device (FV5000), in which the funnel material was changed from cardboard to polypropylene and the number of components was reduced from 8 to 4.

Results

Usability data collected from five clinical studies was used. For each study, a questionnaire on usability consisting of yes-no, open and 5-point Likert scale (very unclear to very clear) questions was completed by the participants using one of both devices. Fisher Exact Test was used to compare usability data from both versions of the Colli-Pee.

Conclusion

Among a total of 371 participants (185 male; 186 female), 46% used CP2000 and 54% FV5000. Colli-Pee was found very easy (70%) and easy (21%) to use, no significant difference between versions was observed (p=0.445). The FV5000 version had less urine spillage during collection: 8% compared to 23% for the CP2000 (p=0.070). Some spillage after collection was present in both devices (11%, p=1.000). The instructions for use were significantly clearer and easier for FV5000 compared to CP2000 (90% vs 65%, p=0.006). 92% of the subjects would like to use Colli-Pee as sample method for

screening purposes (92%, p=1.000) and would recommend it to others (CP2000: 92%, FV5000: 100%; p=0.175). Packaging and recyclability raised a few concerns for both device versions, but the Colli-Pee exists of polypropylene and high-density polyethylene which can be recycled or incinerated into energy. The CP2000 was generally described as hygienic, convenient, women friendly and a good urine collection system with no need to interrupt the urine flow. The improved device (FV5000) was also found suitable for home use and for transportation by regular mail.

References

Usability of the Colli-Pee device was valued as very good and design updates were shown effective through easier assembly of the device before use and reduced spillage of urine during collection. In addition, the current Colli-Pee can be sent by regular mail, making it an easy device suitable for screening purposes.

00392

ACCURACY OF URINARY HUMAN PAPILLOMAVIRUS TESTING AMONG WOMEN REFERRED FOR TREATMENT OF CERVICAL LESIONS: A TECHNICAL PILOT STUDY

10. Self-sampling

M.K. Leinonen [1], K. Beyers [2], S. Biesmans [3], K. Deswert [4], S. Lambin [5], Y. Overmeire [6], M. Poljak [7], G. Schiettekatte [4], S. Van Keer [3], V. Vankerckhoven [2], A. Vorsters [3], M. Nygård [1]

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Background / Objectives

Acceptability of urine sampling is very high for which urinary hrHPV testing could be an alternative to reach previous screening non-responders. We assessed if first void urine specimens are suitable for hrHPV testing and provide reasonable accuracy to detect hrHPV and underlying disease with a given HPV assay as cervical specimens.

Results

We included 10 patients (3 carcinoma, 4 CIN3 and 2 CIN2) referred for treatment of cervical lesion. They completed self-collection using two vaginal devices: a brush (Evalyn®Brush, Rovers Medical Devices, The Netherlands) and a swab (FLOQSwabs™, COPAN, Brescia, Italy) and collected 20ml first void urine using a Colli-Pee™ (Novosanis, Belgium) before their appointment at the hospital where a physician took a cervical specimen. Vaginal and cervical specimens were preprocessed and tested using Anyplex™ II HPV28 (Seegene, Korea), Cobas®4800 HPV test (Roche Molecular Diagnostics, USA) and Xpert®HPV (Cepheid, USA)[1]. Urine specimens were collected without preservative to avoid any interference of the preservative with specimens subject to biobank. Urine was stored at +4C for couple of days before 10ml of urine was centrifuged and rest urine was aliquoted. Aliquots were then kept first at -20C and later on at -80C. Urine aliquots were chosen to have concordant and discordant pairs in cervical and vaginal hrHPV testing. 4.5 ml urine was thawed, mixed with 2.25 ml UCM buffer and aliquoted for

three forementioned assays and for Cobas®6800 HPV test (Roche). Amicon filtration, EasyMag DNA extraction and in-house human DNA quantification (GAPDH) preceded Anyplex™ II HPV28 testing.

Conclusion

Detection of hrHPV in urine tended to be inferior to hrHPV detection in physician-and self-collected cervical cells. Detection of hrHPV in urine varied substantially according to the sensitivity of hrHPV assay being lowest at 40% for Xpert®HPV and highest at 80% for Anyplex™ II HPV28. Viral load in urine usually was lower than in physician-specimen. A brush showed highest concordance with a physician-collected specimen in partial genotyping using all HPV assays. HPV type distribution in different specimen types was similar except for one cancer case which was HPV51 positive in urine and HPV16 positive in cervical and vaginal cells. Furthermore, HPV52 and HPV56 not detected with other collection methods were present as additional HPV types in urine.

References

This pilot study using frozen urine aliquots without preservative does not support full implementation of urinary hrHPV testing. To achieve the most optimal performance, first-void urine is preferred. It should be immediately mixed with preservative to prevent DNA degradation during storage and extraction and, thus, to maximize viral load. Assays with high analytical sensitivity may result in better performance.

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00475

COMPARISON BETWEEN THE SELF-SAMPLING AND URINE FOR THE DETERMINATION OF HPV IN HIGH RISK POPULATION OF OUR MEDIUM

10. Self-sampling

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Background / Objectives

To compare our results in the determination of HPV between spontaneous urine samples versus self-sampling in women who practice prostitution in the province of Almería

Results

Prospective study, approved by the Ethics Committee's H. Torrecárdenas, is divided into two phases, the results of the first phase are shown.

Displacements are made to the different centers where the prostitutes work, we had the help of non governmental organization, after explaining the procedure, they are given an informed consent, a questionnaire is carried out, and they are given a bottle of urine and a swab to perform a vaginal and cervical self-sampling . Subsequently, the determination of HPV in urine is performed, and with the Self-sampling, a study of sexual infection agents, agents related to genital ulcers and determination of the human papillomavirus is carried out, the 14 genotypes studied both in the urine and by the Self-sampling are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The medium used belongs to Werfen and the culture media are: STI essential assay and Genital ulcer Assay. The extraction of HPV DNA has been carried out with the QIASIMPHONI® from Qiagen,

Conclusion

In 51 women who have participated in this first phase of the study, we have seen a prevalence of women with infection of some type of HPV in 25/51(49%), being collected in urine 14/51(27.4%), and in Self-sampling 20/51(39.2%).

The patients who had positive results for urine and Self-sampling at the same time were: 12/51(23.5%). The coincidence in the determination of genotypes between both samples was in: 7/51(13.7%). Patients with genotypes detected in urine and not in Self-sampling: 4/25(16%)

The most frequent genotype in the urine sample was: 16, with 3/51 (5.8%), followed by 51, 58, 33 with 2/51(3.9%) each. The most frequent genotype in the sample by Self-sampling was: 68, with 6/51(11.6%), followed by 16, 66, with 4/51(7.8%), 35, with 2/51(3, 9%).

Patients with infection of more than one genotype were: in Self-sampling, with two 3/20 (15%), with three 2/20 (10%), with four 1/20 (5%). In urine: infection with two: 3/14 (21.4%) with 3 0/20, with 4 0/20.

The viral load was determined qualitatively from + to +++, being generally greater in the Self-sampling than in the sample collected by urine. Self-sampling with broomstick: +++ 3/20 (15%), ++ 13/20 (65%). Viral load in the urine sample: +++ 0/14, ++ 4/14 (28.5%).

References

The prevalence in our sample is higher than that reported in the literature for high-risk population, 24% compared to 49% in our country. There seems to be no high correlation between urine and self-sampling. The Self-sampling does not include all the genotypes that the patient presents. The viral load and the number of genotypes detected by self-sampling is greater than with urine.

00535

Social economic determinants for cervical cancer screening non-attenders offered HPV self-sampling as an alternative to ordinary screening: Who accepted and who did not?

10. Self-sampling

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Background / Objectives

The Copenhagen Self-Sampling Initiative (CSi) offered a HPV self-sampling test as an alternative to cervical screening non-attenders (unscreened > 4 years). In total, 4824 screening non-attenders residing in the Capital region of Denmark accepted and returned a self-sampling brush out of 23.632 invited. To allow for future optimization of self-sampling strategies to recruit screening non-attenders, we assessed socioeconomic determinants of response to self-sampling invitations. Here, we characterize women accepting self-sampling versus women who preferred their own general practitioner (GP) after invitation or remained non-responders.

Results

All women invited for CSi were linked to Statistics Denmark. Logistic regression was used to analyse associations between the socio-demographic information retrieved. The main outcome was divided into: women accepting self-sampling, women screened by GP after invitation to CSi and women not responding at all. Moreover, we dichotomised the group of women who accepted the self-sampling into those returning the brush and those who didn't.

Conclusion

Presented with the invitation for self-sampling, women with non-Danish origin both born (OR=2.07) in and outside (OR=2.05) Denmark were more likely to go to their own GP for a regular screening sample, or ignoring the self-sampling invitation letter (OR=2.17, OR=2.17 respectively) compared women of Danish origin.

For employment and educational level, we found that that women with low educational level (OR=1.29), unskilled workers (OR=1.99), early retirement (OR=2.79) and women on social welfare (OR=2.21) more often ignored the invitation for self-sampling using medium educational level as reference group. In contrast, women with high educational level (OR=1.27), self-employed (OR=1.28), students or women on maternity leave (OR=1.44) more often went to their GP after a self-sampling invitation. Lower income was a determinant of no-reply to the self-sampling invitation (OR=1.82, 1.23 respectively). Women with lower household income were less likely to return the brush despite active acceptance of the self-sampling offer (OR=0.86, 0.89 respectively).

References

Women with low education and/or lower income as well as women of non-Danish origin were the most challenging to recruit for cervical screening for the HPV self-sampling. Initiatives to enhance participation in these groups could include addition of language differentiated information material to the current self-sampling activity.

11. Genotyping

00210

PREVALENCE OF HUMAN PAPILLOMA VIRUS IN VULNERABLE WOMEN FROM BUCARAMANGA COLOMBIA

11. Genotyping

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Background / Objectives

Introduction: Annually more than five hundred thousand women worldwide are diagnosed with cervical cancer[1]. A persistent infection with high-risk Human Papilloma Virus (HR-HPV) is the necessary cause for this cancer[2].

Objetive: To determine the prevalence of the HPV infection in vulnerable women living at the northern district of Bucaramanga, Colombia.

Results

Methods: a survey study was conducted in women between 35 and 65 years old residing in low income areas of the city. Women with moderate or high risk (≥3 points) to develop cervical cancer, determined by a standardized epidemiological survey, were asked to take their own cervico-vaginal samples. In these samples molecular tests were performed by polymerase chain reaction and reverse dot-blot hybridization using HPV CHIP Direct Flow system. Undetermined genotypes were processed again by performing a salting out DNA extraction.

Conclusion

Results: 874 women were surveyed; of these, 469 (53.6%) had moderate or high risk of cervical cancer and took their own samples. The median age was 46 years (RIQ 40-52 years), the median educational attainment was 5 years (RIQ 4-9 years) and the median pregnancy rate was 4 (RIQ 3-5 pregnancies). The prevalence of HPV infection was 11.3% (95% CI: 8.6 - 14.5, n = 53), for HR-HPV was 4.3% (95% CI: 2.6 - 6, 5; n=20), for low-risk HPV (LR-HPV) was 4.1% (95% CI: 2.5-6.3, n=19), for undetermined genotypes was 1.3% (CI 95 %: 0.5 - 2.8, n=6) and for coinfections was 1.7% (95% CI:

0.7-3.3, n=8). The most common HR-HPV genotype was HPV-59 (n=5) and for LR-HPV was HPV62/81 (n=8). We found coinfection with HR-HPV and LR-HPV in six women. Coinfection with two LR-HPV genotypes and with three LR-HPV genotypes occurred in one woman each.

References

Conclusion: The frequency of HR-HPV genotypes found in this study is different from what have been commonly reported by other similar studies. HPV-16 was not the most prevalent genotype and HPV-18 was not found in any of the samples analyzed.

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00331

ASSESSMENT OF ISOTHERMAL AMPLIFICATION AMPFIRE ASSAY FOR DETECTION AND GENOTYPING OF HPV IN FORMALIN-FIXED PARAFFIN-EMBEDDED HEAD AND NECK CANCER SAMPLES

11. Genotyping

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Background / Objectives

Infection with high risk HPV is etiologically linked to a group of oropharyngeal squamous cell carcinomas (OPSCCs) that show better clinical outcome and response to treatment. The identification of HPV-related tumours in the clinical setting is mainly based on the detection of $p16^{INK4A}$ overexpression. However, the combination of $p16^{INK4A}$ overexpression and HPV DNA testing increases diagnostic accuracy and have a better prognostic value. HPV-DNA detection platforms are usually expensive, require well trained staff and have been designed for a high-throughput workflow, hampering its implementation for OPSCC diagnosis and raising the need for rapid and cheap molecular methods for low and middle income countries. The aim of this study was to assess the AmpFire HPV Test (Atila Biosystems), a simple, fast and low cost HPV DNA assay, for formalin-fixed paraffin-embedded (FFPE) samples.

Results

Two batches of samples were assayed using the AmpFire test. The first batch comprised 56 OPSCC samples from the head and neck ICO international collection (1950-2009). Longstanding remaining DNAs extracted from these samples by Proteinase K digestion, had previously been used to perform a SPF10/DEIA/LiPA25 HPV test. Also, 105 head and neck tumour FFPE samples collected during 2016-2018 at Hospital de Bellvitge, were extracted by Maxwell 16 FFPE Plus LEV DNA Purification kit and tested using the Roche Linear Array HPV Genotyping test. Viral DNA was amplified and detected in a CFX96 real time qPCR instrument using a 60ºC isothermal reaction for 74 min. The AmpFire Test allows real time fluorescent detection of 15 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) and individual genotyping of HPV16 and 18.

Conclusion

Out of 56 samples from the ICO international collection, 5 were HPV positive, 29 were negative and 23 were invalid (fail in β-globin gene amplification). This data represents a 93% agreement with SPF10/DEIA/LiPA25 results. To avoid the high rate of invalid tests, probably due to aged samples and DNA degradation, we analysed 105 recent FFPE samples. HPV-DNA was found in 30 out of 105 samples, 74 were negative and 1 was invalid, showing a 96% agreement with Linear Array HPV Test and a kappa index of 0.923 and 100% concordance for the presence of HPV16 and 18.

References

Preliminary data have shown that AmpFire HPV Test is a sample-to-answer and low cost assay for detection and genotyping of HPV in FFPE oropharyngeal samples recently collected that exhibits high agreement with data assayed by SPF10/DEIA/LiPA25 and Linear Array HPV tests.

00451

PERFORMANCE OF THREE HPV GENOTYPING ASSAYS ON FORMALIN-FIXED PARAFFIN-EMBEDDED CERVICAL SAMPLES

11. Genotyping

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Background / Objectives

HPV genotyping of formalin-fixed paraffin-embedded (FFPE) cervical tissue material is important for epidemiological research, vaccine surveillance and for clinical purposes. In this study, the performance of three HPV genotyping assays will be evaluated.

Results

A total of 80 cervical FFPE samples from 61 patients with high-grade (CIN2 n=10; CIN3 n=38, with biopsy vs cone material from 19 patients; ACIS n=9) and cancer lesions (SCC n=12; AC n=11) were included in the study. Four sections of 5 µm from each paraffin block were prepared for DNA extraction, with hematoxylin and eosin (HE) sections before and after. DNA extraction was performed by using the QIAsymphony DSP DNA Mini Kit. Sample adequacy was evaluated by beta-globin PCR. The presence of HPV was assessed by PCR using modified general primers (MGP) followed by type-specific hybridization by Luminex technology, detecting and genotyping 37 HPV types, and Anyplex HPV28 (Seegene), detecting and genotyping 28 HPV types. HPV negative samples were analyzed with in-house E6/E7 type-specific PCR for the 14 high-risk HPV types. This assay will also be used for verification of discordant genotype results. Illumina next generation sequencing of MGP amplicons will be performed on all samples.

Conclusion

In total, 72 of 80 samples (90%) were found HPV positive with Luminex (66/72) and/or Anyplex HPV28 (69/72); eight samples (10%) were negative/invalid by both methods. Multiple infections were found in 14 samples, of which six were reported as single infections with Luminex and one as negative with Anyplex. Single infections identified by both assays (n=50) showed full concordance. Altogether, 26 of the 38 genotypes covered by the two assays were identified. High-risk HPV types were detected in 68 samples, representing all high-risk types except HPV56. Three patients were found positive for genotypes other than the 14 high-risk types (HPV40, AC; HPV42/53, CIN3; HPV70, SCC). Of the eight samples negative/invalid by both assays, six were found positive with E6/E7 type-specific PCR; findings on HR sections may explain the two triple negative samples.

References

This study shows that both Luminex and Anyplex HPV28 reliably detect HPV in FFPE samples, with Anyplex HPV28 showing a slightly higher sensitivity. We further recognize the value of applying extended genotyping to the high-risk types, although this primarily will contribute in finding multiple infections. Discrepancy in high-risk HPV sensitivity and specificity (n=14) will be verified with E6/E7 type-specific PCR. Correlations including data from next generation sequencing will be presented.

00509

RETROSPECTIVE ANALYSIS OF THE HPV GENOTYPE AND ESTIMATED IMPACT OF THE VACCINE AGAINST HPV IN SOUTHERN SPAIN

11. Genotyping

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Background / Objectives

Persistent infection of high-risk human papilloma virus (HR-HPV) is thought to be responsible for about 100% of cervical cancer cases. To reduce the incidence of these pathologies, mainly of cervical cancer, several vaccines against HPV have been developed: a bivalent vaccine against HPV 16 and 18 (with some cross-protection against HPV 31, 33 and 45) and a quadrivalent vaccine against genotypes HPV 6, 11, 16 and 18. In Andalucia (Spain), the bivalent vaccine was introduced in the official immunization schedule for girls at the end of 2008. Three doses (0–1–6 months) were administered to girls born after the 1st of January of 1994 when they were 14 years old. The objective of this study was to estimate the impact of HPV vaccine through retrospective analysis of the distribution of HPV genotypes in local area of Cadiz, southwest of Andalucía.

Results

We studied 1272 women in the period 2009-2018, stratified by age in two groups: 17 to 23 years (489) and 24 to 48 years (823). The patients, included in an opportunistic protocol for cervical cancer screening, were studied retrospectively in two time periods: from 2009 to 2013 (819) and from 2014 to July 2018 (453). Only samples with a positive result for at least one HPV genotype were included in the study. HPV genotype was determined with CLART HPV2 (Genomica) until 2013 and Anyplex II HPV28 (Seegene) in 2014.

Conclusion

HPV 16 was detected between 2009 and 2013 in 125 women under 23 years of age (33.9%). This proportion has been reduced to 7.5% (9 women) in the 2009-2013 period. In women with 24-28 years of age, the proportion remains constant in both

periods (26.7%). There are also significant reductions in the detection of HPV 18 (11.1% vs 2.5%) in women under 23 years of age. The detection of HPV genotypes 31, 33, 45, 51, 52 and 58 have remained without significant changes. Unlike what happens with high-risk genotypes, an increase in the detection of low-risk genotypes can be observed, such as HPV 6 (34.2% vs. 14.6%) and HPV 42 (26.7% vs. 11.4%).

References

In summary, the retrospective analysis of samples studied in the last ten years seems to indicate a significant decrease in the genotypes included in the vaccine administered since 2008. However, this effect is not contemplated in high-risk genotypes not included in the vaccine and there is a significant increase in low risk genotypes, associated with an increase in the appearance of other sexually transmitted infections in a younger population. The study has the limitation of its retrospective character and the opportunistic obtaining of the sample, but it can indicate an interesting tendency that it is necessary to confirm with studies designed for that purpose.

12. Molecular markers

00051

Detection of potential biomarkers in the high grade anal intraepithelial neoplasia from HIV/HPV co-infected MSM

12. Molecular markers

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Background / Objectives

MCL-1, Exportin-5, and Importin-beta expression in anal intraepithelial neoplasia (AIN) in Man who have sex with man (MSM) that are HIV-infected is poorly characterized. The aim of this pilot study was to analyze the expression of these proteins as well as in situ HPV DNA and E6/7 RNA in high grade AIN.

Results

Immunohistochemistry was used to analyze the expression of MCL-1, Exportin-5, and Importin-beta. HPV DNA was detected with the Enzo polybiotin assay and HPV E6/7 RNA detected in situ via the ACD assay. A total of 10 anal biopsy specimens from HIV/HPV co- infected MSM were analyzed

Conclusion

Each lesion showed AIN 2-3. HPV DNA was detected in all layers of the dysplastic lesion, though higher copy towards the surface. HPV RNA localized primarily to the cells in the upper (differentiated) layer of dysplastic lesion. MCL1, importin-beta, and exportin-5 localized primarily to the more basal (undifferentiated) layer of the AIN.

References

AIN2-3 lesions show low copy HPV DNA that co-localizes with MCL1, importin-beta, and exportin-5 in the more basal, less differentiated area of AIN. As the cells differentiate towards the surface, they show higher copy HPV DNA, HPV E6/7 RNA,

and lose the expression of MCL1, exportin-5, and importin-beta. The data suggests that MCL1, exportin-5, and importin-beta proteins may have an important role and may be useful biomarkers of high grade AIN.

00055

Meta-analysis of the accuracy of p16 or p16/Ki-67 immunocytochemistry versus HPV testing for the detection of CIN2+/CIN3+ in triage of women with minor abnormal cytology

12. Molecular markers

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Background / Objectives

Consistent evidence shows that women with atypical squamous cells of undetermined significance (ASC-US) can be triaged appropriately with a high-risk (hr)HPV test. However, triage of low-grade intraepithelial lesions (LSIL) with hrHPV testing is problematic due to its very low specificity. Overexpression of p16, with or without Ki-67 and identified through immunocytochemistry, indicates neoplastic transformation of HPV-infected cervical cells and may predict more accurately underlying cervical intraepithelial neoplasia of grade 2 or worse (CIN2+).

Results

A literature search was conducted in three bibliographic databases. Studies were selected if they included women with ASC-US or LSIL who were triaged with dual staining (p16/Ki-67) and/or p16 staining and, if available, with a comparator hrHPV test to detect CIN2+.

Conclusion

Thirty-eight studies published between 2005 and 2017 were found eligible. The pooled sensitivity of p16 staining to detect CIN2+ was 82% [95% CI, 76-87%] and 83% [76-88%] in triage of ASC-US and LSIL, respectively, whereas the pooled specificity was 71% [65-76%] and 62% [52-71%], respectively. The pooled sensitivity of dual staining was 84% [77-89%] and 86% [82-89%] for ASC-US and LSIL, respectively, and the pooled specificity was 77% [70-82%] and 66% [59-72%], respectively. Six hrHPV DNA tests, used as comparator tests, did not show inter-test

heterogeneity. The sensitivity of p16 staining was significantly lower compared to hrHPV DNA testing (ratio=0.90 [0.84-0.96] and ratio=0.84 [0.80-0.89] in case of ASC-US and LSIL, respectively). In contrast, the specificity of p16 staining was substantially higher with a relative specificity of 1.60 [1.35-1.88] and 2.29 [2.05-2.56], in case of ASC-US or LSIL, respectively. Dual staining was also significantly less sensitive than hrHPV DNA testing (ratio=0.90 [0.84-0.97] and ratio=0.90 [0.87-0.94] for ASC-US and LSIL, respectively), but more specific (ratio=1.65 [1.42-1.92] and ratio=2.45 [2.17-2.77] for ASC-US and LSIL, respectively). Dual staining and p16 staining were equally sensitive and specific with regard to LSIL triage. For ASC-US triage, p16 showed similar sensitivity but was significantly less specific (ratio=0.87 [0.76-0.99]) than dual staining.

References

This meta-analysis has demonstrated that there is a loss in sensitivity with dual staining and p16 compared to hrHPV DNA testing in triage of ASC-US and LSIL, but there is a gain in specificity, especially in LSIL triage. Among the staining methods there was no difference in accuracy, except for the specificity of p16 alone, which was lower in the triage of ASC-US.

00186

P16 IN THE HISTOLOGICAL DIAGNOSIS OF THE INTRAEPITHELIAL NEOPLASIAS OF THE CERVIX: EVALUATION AND PROPOSALS FOR USE.

12. Molecular markers

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Background / Objectives

It is known the low agreement between pathologists when diagnosing grade 2 cervical intraepithelial neoplasia (CIN2), an important diagnosis, given that its clinical management is very often an excisional treatment. The LAST project proposes the application of a binary classification (high or low grade lesions) to diagnose cervical pre-neoplastic lesions and facilitate their clinical management, follow-up (low grade) versus treatment (high grade). LAST proposes the use of the p16 protein to improve the agreement between pathologists and as an aid in difficult cases, with diagnostic doubt low / high grade, frequently assigned to CIN2. As published in the literature, p16 is a technique that is easily performed and interpreted, with good agreement between pathologists. It is true? Do pathologists need specific training to adequately capitalize on the use of p16 under this indication?

Results

Three general pathologists with more than twenty years of experience were asked, one of them with special dedication to the field of gynaecology, who evaluated 132 biopsies stained with p16, from haematoxylin eosin (HE) of biopsies previously diagnosed as CIN2. The pathologists were only given the cuts stained with p16, without their HE. In each case, a cut dyed with p16 and its corresponding internal control. The sections stained with p16 were accompanied by an explanatory document (Bergeron) on how to evaluate the biopsies: positive those cases with intense and diffuse staining that affects the entire thickness of the epithelium, and negative the rest of the cases.

Conclusion

The percentage of positivity for each pathologist was variable:Pathologist(P)1:76,3% P2:76,6% P3 61,5%

The agreement between them: P1/P2 0,82(Kappa:K) P1/ P3: 0,649 P2/P3 0,625

When comparing these results, with important series of the literature:

Meserve:0,73 Galgano:0,87 Bergeron:0,89(K)

It is verified that in the comparisons that involve the pathologist 3, we move away much from the expected results. These differences may be due to the difficulty in interpreting the positivity, or to the different criterion of the pathologist 3, since it is markedly different from the other two. We have considered only two options, positive or negative, but there are diverse proposals, frequently used, that provide intermediate positivity criteria based on the percentage of positive cells, and others that consider the intensity of positivity. In short, there is no consensus in the reading and subsequent report of p16 stains

References

It is necessary to establish standardized criteria of positivity of the technique, and to provide pathologists with previous training that has an impact on the correct interpretation of the biopsy and, ultimately, on a better clinical management of the patients.

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00208

XRCC1 rs1799782 and ERCC2 rs13181 POLYMORPHISMS AS POTENTIAL PROGNOSTIC AND PREDICTIVE FACTORS IN CERVICAL CANCER PATIENTS

12. Molecular markers

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Background / Objectives

Cancer cells efficiently repair treatment-induced DNA damage, exhibiting greater resistance to radiation or DNA damaging agents. Cervical cancer is commonly treated by platinum-based chemoradiotherapy, and the inactivation of DNA repair may increase the efficacy of treatments. Given that genetic polymorphisms seem to influence the repair capacity of tumor cells and can be identified by using blood samples, they are promising biomarkers in the clinical decision-making process for cancer patients. Thus, the aim of present study was to assess the prognostic and predictive values of XRCC1 rs1799782 and ERCC2 rs13181 polymorphisms in cervical cancer patients.

Results

This retrospective hospital-based study includes a total of 260 Caucasians patients with histologically confirmed cervical carcinoma (FIGO stage IB2-IVA). The patients were recruited between February 2002 and October 2009 and treated with cisplatin-based concomitant chemoradiotherapy in Portuguese Institute of Oncology of Porto. The genotyping was performed using Taqman™ Allelic Discrimination methodology by Real-Time PCR. Difference in frequencies of the genotype between the different therapy responses groups were evaluated by $\chi 2$ test. Overall survival (OS) and disease-free survival (DFS) were estimated by Kaplan-Meier method and log-rank test. A level of $P<0.05$ was considered statistically significant.

Conclusion

There were no significant statistical differences between the different genotypes of the XRCC1 rs1799782 and ERCC2 rs13181 polymorphisms and treatment response ($P=0.738$ and $P=0.805$, respectively). Concerning the OS, we observed that patients with advanced disease, negative lymph nodes metastasis (LNM) and carriers of ERCC2 CC genotypes present a higher survival when compared with carriers at least one A allele (AA/AC genotypes) ($P=0.020$). Additionally, we verified that carriers ERCC2 CA/AA genotypes carrier patients present a risk of death of approximately 9 times higher than patients with the CC genotype, adjusted for LNM prognostic factor ($P=0.030$; $P=0.029$, bootstrap analysis).The results also showed that patients group with stage IIb or higher, age above 39 years old and carriers of ERCC2 CC genotypes present a statistically significant lower risk of developing relapse than CA/AA genotypes carrier patients ($P=0.040$).

References

In conclusion, we demonstrated the clinical significance of polymorphisms in DNA repair genes in cervical cancer patients. The ERCC2 rs13181 polymorphism might be used as a prognostic marker for patients undergoing cisplatin-based chemoradiotherapy. However, additional studies are required for validation these results.

00281

IS RNA EXTRACTION METHOD CRUCIAL FOR HUMAN PAPILLOMAVIRUS E6/E7 ONCOGENES DETECTION?

12. Molecular markers

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Background / Objectives

The aim of the present study was to study the relationship between HPV E6/E7 oncogenes mRNA expression and cervical cancer development in women population in Basque Country (Spain) and compared three RNA extraction methods to evaluate its impact in mRNA expression.

Results

Samples were genotyped by Linear Array genotyping Test. RNA extraction was performed using three RNA extraction methods: NucliSENS kit (bioMérieux), High Pure Viral RNA kit (Roche) and RNeasy Plus Mini kit (Qiagen). HPV16, 18, 31, 33 and 45 high-risk genotypes E6/E7 mRNA was detected by NucliSens® EasyQ® HPV v1 Test (Biomerieux). Finally, E6/E7 mRNA and pathology were studied over time. Pathology was classified in three groups: 1) normal, 2) ASCUS (Atypical squamous cells of undetermined significance) and low-grade cervical intraepithelial neoplasia (CIN1) and 3) High-grade cervical intraepithelial neoplasia (CIN2/CIN3).

Conclusion

mRNA E6/E7 positivity rate was: 62% with NucliSENS kit, 24% with High Pure Viral RNA kit and 6% with RNeasy Plus Mini kit. Because of low positivity rate with RNeasy Plus Mini kit, this was discarded for further analysis. Genotype 33 was the most expressed followed by 18.

mRNA expression was higher in patients with lesion and progression of the lesion than the group that not presented lesion or persistence of the lesion.

NucliSENS and High Pure Viral RNA extraction kits showed similar negative predictive value (73.68% and 65.79%, respectively), but positive predictive value was higher with High Pure Viral RNA extraction kit (75%). NucliSENS extraction kit

showed lower specificity than High Pure Viral RNA extraction kit (89.28% vs. 50%) but higher sensitivity (77.27% vs. 40.90%).

References

NucliSENS extraction method was more concordant to detect women with lesion and seems to be more suitable with progression of lesion. High Pure Viral RNA extraction method was more appropriate to discard women without progression of lesion and was more appropriate for screening of cervical cancer due to its high specificity.

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00289

COULD METHYLATION ASSAYS FOR EARLY DETECTION OF CIN2+ LEAD TO OVERTREATMENT? – CASE REPORT

12. Molecular markers

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Background / Objectives

The connection between persistent HPV infection and cervical cancer is well established. The most recent challenge is to make an early differential diagnosis between transient infections from those that will develop into CIN 3 or cervical cancer. Tests were developed based on knowledge underlying molecular mechanisms of oncogenic expression that allow the clinician to distinguish benign HPV infections from those that progress to precancer, making an early identification of patients who could benefit from treatment from those who are better off with no intervention.

The authors present a case of a G1 P1 45 year-old-woman referred to consultation due to a positive oncogenic HPV33 test result and a liquid-based cytology (LBC) NILM, with a T3 transformation zone (TZ) colposcopy.

Results

This patient had a previous history of loop excision biopsy technique (LEEP) 8 years before due to CIN2. She was submitted to a second LEEP one year after the first one due to persisting positive oncogenic HPV (not 16/18 – hybrid capture II) and T3 TZ colposcopy. Histology revealed CIN 1. She was discharged two years after the second LEEP with negative oncogenic HPV test results (hybrid capture II) and NILM LBC. When she was referred to our consultation with a positive oncogenic HPV result (HPV genotyping seegene) and NILM LBC, a colposcopy was performed which was unsatisfactory (T3 TZ); a methylation specific real-time PCR assay (GinTect®) was requested in order to ascertain whether or not methylation was present in six different DNA regions that correlate with the presence of pre-cancerous or cancerous cervical lesions. This test was positive, showing alterations in 4 out of 6 DNA regions.

References

The clinician was facing a rather anxious woman who demanded immediate treatment. So, within this context, she was submitted to a new LEEP, which confirmed a CIN 1. The authors are aware that expectant treatment would have been the best approach in this scenario, due to the fact that this was probably a new contact with a positive oncogenic HPV test result with NILM LBC. Nevertheless, in face of her previous history, a methylation assay was considered in order to convey an additional advantage on the detection of a CIN2+ cervical lesion. This is an interesting case because both LBC (NILM result) and methylation assay (positive test) showed a discordant result from the definitive histological result. The authors present it in order to expose the complex management of these patients and the importance of the clinician's awareness of the positive and negative predictive values of these tests.

00337

DETECTION OF HIGH RISK HPV TYPES AND RISK PREDICTION OF CERVICAL CANCER

12. Molecular markers

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Background / Objectives

Most hrHPV infections are transient and regress at a very high frequency within 1-2 years.The malignant progression of hrHPV infections to detectable tumours is often a slow process that can arise in few years to decades after the original infection. In general, the detection of hrHPV virus (DNA) in cervical cellular samples allows earlier diagnosis before the development of cervical cancer (CC) as compared to cytology, but it does not allow the distinction between transient and risky persistent infections leading to CC. Thus, using such a test as a standalone diagnostic tool in CC screening would result in overdiagnosis and overtreatment as transient hrHPV infections are extremely common in sexually active individuals. Hence, the presence of hrHPV DNA alone is not enough to determine the risk of developing CC; the integration of the virus genome within the host genome appears to be the main deriver in triggering the induction of viral oncogenes (E6/E7) leading to instability of the host cells and oncogenesis. GeneFirst has already developed a first line screening assay that detects and differentiates DNA or 14 hrHPV types. In this study, we are developing an RNA-based triage assay for the assessment of the risk of CC development due to hrHPV infections.

Results

The predictive triage IVD is secondary qualitative genotype-specific diagnostic assay. The assay is designed to detect specific-transcripts of viral E6/E7 oncogenes, biomarkers for the onset and progression of host cell instability and oncogenesis associated with hrHPV infections. The assay can specifically distinguish transcripts of the oncogenes for all the 14 hrHPV types identifiable by the Papilloplex® Kit. The triage IVD is a single tube PCR assay based on the MPA technology. All individuals who test positive by this assay are recommended to undertake thorough medical investigations checking for changes in the appearance of cervical squamous and epithelial cells. This assay includes internal controls for sample cellularity and PCR inhibition.

References

The combination of a primary DNA screening and a triage to detect viral-specific oncogenic biomarkers will allow earlier detection of CC as compared to cytology (Pap smear) and will help in avoiding overdiagnosis as compared to current DNA-based diagnostic tools. In addition, the use of our combined devices will significantly reduce costs to health systems; for unnecessary overtreatment and follow up investigations in women with harmless infections. Hence the designed IVDs allow for reliable implementation of self-collected cervical cellular samples, this will improve the CC screening coverage, by reducing refusal to participation due to embarrassment associated with the involvement of medical staff in collecting the samples.

References

00397

Inter-observer agreement on interpretation of dual stained p16/Ki-67 samples in a HPV positive primary screening population

12. Molecular markers

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Background / Objectives

Dual staining for p16/Ki-67 is recognised as a potential triage test for women with a HPV positive primary screening test. This study examines the reproducibility of p16/Ki-67 dual stain interpretation among three slide reviewers.

Results

In partnership with CervicalCheck, The National Cervical Screening programme, CERVIVA are undertaking a longitudinal observational HPV primary screening study which is evaluating different triage strategies for management of a HPV-positive primary screening test. As part of this ongoing study dual staining for p16/Ki-67 (CINtec PLUS) was performed on 841 primary screening samples that tested positive for HPV (cobas 4800 HPV test). Three reviewers, including two cytopathologists and one individual with advanced training and experience with p16/Ki-67, independently reviewed a subset of 245 cases. A sample was deemed positive by the presence of one or more dual stained cells in a specimen. The results were compared to determine inter-observer agreement.

Conclusion

The proportion of cases interpreted as positive by each reviewer ranged from 29.1%-43.8%. There was consensus agreement between all three reviewers for a positive or

negative result in 77.0% of cases. Agreement between reviewer 1 and 2 was 79.7% (Kappa 0.538; 0.420-0.685), reviewer 1 and 3 was 78.7% (Kappa 0.558; 0.431-0.685) and reviewer 2 and 3 was 81.6% (Kappa 0.605; 0.478-0.733). Disagreement amongst reviewers was most commonly seen in cases with weak staining intensity for p16 or Ki-67 and samples with a very low number, 1-2 cells, of dual positive cells present on the entire slide. Discordant results will be subject to pathologist review.

References

These preliminary findings show that the reproducibility of interpreting p16/Ki-67 dual stained slides is moderate between three reviewers. These findings suggest that with adequate training dual staining for p16/Ki-67 can be incorporated in to routine cytology laboratories.

00431

CERVICAL CANCER CELL LINES MEMBRANE PROTEOMICS OFFER NEW INSIGHTS IN THE DISEASE MECHANISMS

12. Molecular markers

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Background / Objectives

Cervical cancer is the fourth most common malignancy in women worldwide and while its incidence and mortality are declining in developing countries, the available therapeutic approaches can seriously affect the fertility of the patients. Thus, there is a pressing need for less toxic and targeted therapies. The membrane proteome is a potential source of therapeutic targets; however, despite the significance of membrane proteins in cancer, proteomic analysis has been a challenging task due to their unique biochemical properties. The aim of this study was to develop an efficient membrane protein enrichment protocol and to compare the expression pattern of membrane proteins of one normal (HCK1T) and three cervical cancer cell lines, C33A (HPV-), SiHa (HPV16+), and HeLa (HPV18+), in order to discover proteins which are involved in cervical carcinogenesis and may constitute novel drug targets.

Results

A novel reproducible protocol for membrane protein isolation and enrichment was developed, involving differential ultracentrifugation and detergent-based solubilization. LC/MS-MS proteomics and bioinformatics analysis were performed in the membrane fraction of the cervical cell lines.

Conclusion

The percentages of membrane and transmembrane proteins in our enrichment protocol were significantly higher compared to the corresponding data derived from total cell extract analysis. Differentially expressed proteins were detected by the comparison of cervical cancer cell lines with the normal cell line. Among these, the most notable membrane proteins include thioredoxin-related transmembrane protein 2, constitutive coactivator of PPAR-γ-like protein 1, cleft lip and palate transmembrane protein 1, nicastrin and cytoskeleton-associated protein 5. While these membrane proteins have not been reported in previous cervical cancer studies, published reports support their involvement in other cancer types. Bioinformatics analysis revealed that the differentially expressed proteins participate in biological pathways relevant to malignancy, such as HIPPO signaling, PI3K/AKT Signaling, Cell Cycle: G2/M DNA Damage Checkpoint Regulation and EIF2 Signaling.

References

An efficient and reproducible protocol for membrane proteomics analysis was developed, resulting in the identification of a significant number of unique membrane proteins relevant to cervical cancer. These unique membrane protein identifications, offer insights on a previously inaccessible part of the cervical cancer proteome and may represent putative diagnostic and prognostic markers, and eventually therapeutic targets.

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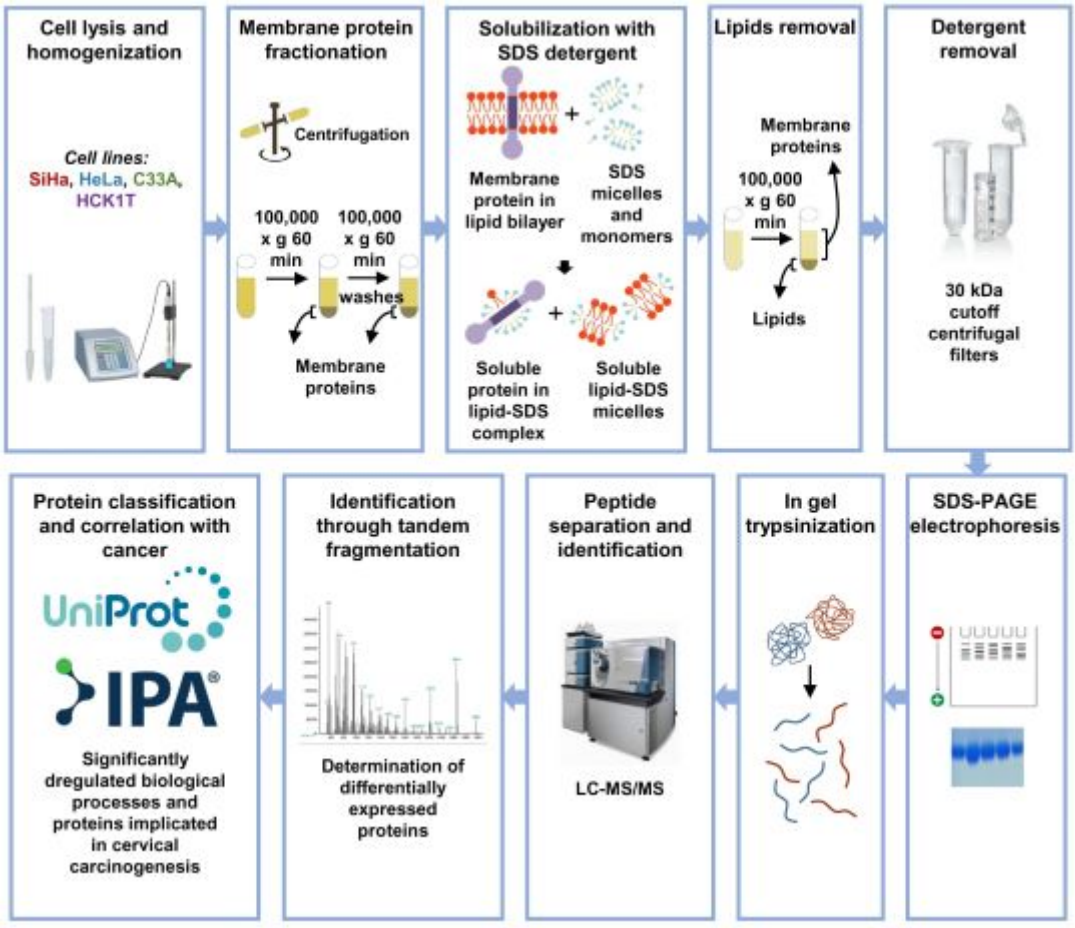

00471

EXPRESSION AND CLINICAL SIGNIFICANCE OF ANGIOPOIETIN-1, ANGIOPOIETIN-2, TIE2 RECEPTOR AND HPV STATUS IN PATIENTS WITH PENILE CARCINOMAS

12. Molecular markers

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Background / Objectives

Background/objetives. Penile carcinoma (PC) is a rare cancer and HPV infection is one of the risk factors for this disease. Little is known about the prognostic markers for PC. The aim of this study was to evaluate whether angiopoietin/Tie2 gene expression influence clinical outcome, HPV status and survival rates in patients with penile carcinoma.

Results

Methods. Quantitative real time polymerase chain reaction (qPCR) was performed to evaluate Angiopoietin-1, Angiopoietin 2 and Tie2 receptor gene expression in a group of 53 penile carcinoma specimens. The commercial kit INNO-LiPA (Fujerebio) was used to detect and genotype HPV. Gene expression was investigated in association with clinical-pathological parameters, HPV status and patient's survival rates.

Conclusion

Results. Lower expression of angiopoietin 1 was associated to Jackson stage III (p=0.001) and inguinal relapse after surgery (p=0.019). Patients with higher Ang1 expression presented higher survival rates (p=0.037). Ang2 expression was lower in patients with deep tumor invasion (p=0.011). Tie2 was not associated to any of the evaluated clinical parameters. The prevalence of HPV in the group was 35.9% and 71.4% of the positive cases were HPV 16 or 18. HPV infection was associated with high Ang1 expression (p=0.029)

References

Conclusions. In the current study we have shown that Angiopoietin 1 is a biomarker for better prognosis in penile cancer. High risk HPV 16 and 18 were found in most of the infected samples, showing its importance in the development of PC. Further studies, are necessary to evaluate the exact role of angiopoietin/tie2 pathway associated to HPV status in penile carcinoma. These findings could possibly guide more precisely surgical treatment and target therapies in penile cancer.

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13. Screening methods

00025

COVERAGE OF PAP TEST AND ADHERENCE TO ALTERNATIVE METHODS OF CERVICAL CANCER PREVENTION IN BARRETOS CITY, SÃO PAULO: PRELIMINARY RESULTS FORM A POPULATION-BASED STUDY

13. Screening methods

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Background / Objectives

Cervical Cancer (CC) is a serious public health problem in Brazil and the coverage rates of the Pap test, the incidence and mortality due to the disease remain high, and non-adherence to screening and periodic screening is involved in late diagnosis.

Objective: To estimate the prevalence and adherence to the Pap test in women aged between 25 and 64, to verify the proportion of women adherent to the program and offer 5 options of cervical cancer screening exams.

Results

Methods: A population-based study, where the Census Sectors were selected, comprising the urban area of the Municipality of Barretos and the sample plan by cluster. We divided the proportion of heads of households into income and literacy and the census tracts were divided into 9 strata, named "A" to "I". This stratification was made to represent the individuals belonging to different socioeconomic strata of the population to be included in the study. In this sense, 2,400 women between 25 and 59 years old will be included, with 1920 who never did or did not have the Pap test for more than 3 years, randomized into 5 groups of alternative exams (384 women in each group): Group 1- women invited to a Pap test and HPV screening at the Barretos Cancer Hospital (BCH) Prevention Department; Group 2- to the women were invited to a Pap test and HPV screening in the Mobile Unit; Group 3- women were asked to collect urine at home for HPV screening; Group 4- in this group women self- collected samples at home for HPV test; Group 5- women choose

between Pap test in the BCH Prevention Department, Pap test in the Mobile Unit, urine collection or self-collecting in the home. For groups 3 and 4 will was also be offered the Pap test that is the official recommendation of the Ministry of Health of Brazil.

Conclusion

Preliminary Results: To date, 333 residences were visited, 175 women were included in the study. 82 (46.8%) did not know what a Pap smear was, 43 (25.7%) never did or did not take the Pap test for more than 3 years, 8 women had never taken the exam in their lives and reported that they did not do it out of ignorance, carelessness, did not feel sick and out of shame. Of these, 38 (88.4%) accepted one of the alternative methods of prevention.

References

Conclusion: This ongoing study is evaluating noncompliance with the Pap test and proposing alternatives to overcome the cultural, moral, education and access to health barriers by comparing adherence to other collection methods for CCU prevention.

00044

Suitability of the training program for evaluation of p16/Ki-67 staining for laboratory staff without skills in gynecological cytology and immunocytochemistry

13. Screening methods

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Background / Objectives

For the purpose of the Slovenian Cancer Screening Program ZORA we developed a training program for the evaluation of p16/Ki-67 immunocytochemical staining (ICS) on conventional PAP smears. We aimed to test if this program is also suitable for teaching laboratory staff without skills in gynecological cytology and ICS.

Results

The training program was tested on two students (Ss), biologist (S1) and medical doctor (S2) who had no prior knowledge in gynecological cytology and ICS. The p16/Ki-67 ICS slides and staining results (reference, R) used for training were from the L3-5512 project. The training program consisted of two parts: 1. lectures, teaching slides and evaluation of 118 p16/Ki-67 ICS slides; 2. discussion of 118 p16/Ki-67 ICS slides with discordant results on multihead microscope. After the training qualification the Ss were tested with 383 p16/Ki-67 ICS slides. All slides were reevaluated by senior cytotechnologist (SC). Exact agreement, Kappa statistics, sensitivity and specificity for CIN2+ were calculated for the Ss and SC and compared to R.

Conclusion

The agreements of pairs of evaluators (S1/SC; S2/SC; S2/R) for p16/Ki-67 ICS interpretation increased from 82.2%, 83.1% and 83.8% (Kappa 0.57, 0.57, 0.61) to 85.4%, 85.9% and 85.4% (Kappa 0.71, 0.70, 0.68) after the second part of the training, respectively. The agreement between S1 and R decreased from 81.0% to 75.5% (Kappa from 0.55 to 0.52). Sensitivity for CIN2+ decreased for both Ss (from 97.1% and 95.7% to 87.0% and 84.4%) with the increase of specificity (from 36.7 and 42.9% to 63.7% and 78.8%). However, the sensitivity (87.0%) and specificity

(80.4%) of R were still better than those of both Ss. The difference was not significant.

References

Ability of Ss for p16/Ki-67 ICS interpretation improved during training. Their specificity for detection CIN2+ has substantially increased with reasonable decrease of sensitivity. Due the suboptimal specificity further supervision by SC is recommended.

00518

Diagnostic concordance between cytology, colposcopy and biopsy in cervical pathology in Funchal, Portugal

13. Screening methods

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Background / Objectives

The aim of the study is to determine the diagnostic concordance between cytology, colposcopy and biopsy in patients with cervical abnormalities.

Results

A retrospective study was performed in the period between September/December 2017. Inclusion criteria was patients that have been submitted to cervical biopsy due to abnormal cytological findings in Hospital Dr. Nélio Mendonça's Cervical Pathology Department (HDNMCPD). All the cytologies and biopsies were interpreted in the Hospital's Pathology Service; the colposcopies performed by two experienced colposcopists; the biopsies were obtained from de suspected areas of the cervix during colposcopy. Data was collected from individual patients hospital records.

Conclusion

In the study period (Set 2017-Dec 2017), in HDNMCPD, 75 women have been submitted to a cervical biopsy in consequence of an altered cytology result that motivates subsequent colposcopy examination prior to biopsy. Mean age was 42.6 years (min. 22, max. 87) with a mean Body Mass Index (BMI) of 27.3. The elapsed time between cytology and biopsy was 174 days, on average. Eight cases were excluded due to inconclusive colposcopy (N=2) or insufficient or inconclusive biopsy sample (N=6). The results of the cytologies that led to the biopsies were: 10.4% atypical squamous cells of undetermined significance (ASC-US), 32.8% atypical squamous cells cannot exclude HSIL (ASC-H), 29.9% low-grade squamous intraepithelial lesions (LSIL), 22.4% high-grade squamous intraepithelial lesions (HSIL) and 4.5% atypical glandular cells not otherwise specified (AGC-NOS) according to the Bethesda classification. Colposcopies were classified with the International Federation of Cervical Pathology and Colposcopy (IFCPC) terminology: 68.7% for grade 1 (minor), 28.3% for grade 2 (major) and 3.0% for suspicious for

invasion. Biopsies results were classified in: 34.3% without dysplasia, 29.9% LSIL, 32.8% HSIL and 3.0% superficially invasive squamous cell carcinoma (SISCCA), according to the Lower Anogenital Squamous Terminology (LAST) classification. We found an incidence of cervical dysplasia of 65.7% (45.5% LSIL; 50.0% HSIL; 4.55% SISCCA). In the biopsy group classified as LSIL a concordance of 50.0% was found between cytology-colposcopy-biopsy. In the biopsy group classified as HSIL the triple-test concordance was higher with a percentage of 72.7. For the SISCCA group there was no concordance. Global agreement cytology-colposcopy-biopsy was 38.8%. The concordance found between colposcopy-biopsy was 55.2%, higher than the 44.8% found between cytology-biopsy.

References

The concordance found between cytology-colposcopy-biopsy was moderate (38.8%).

00591

Evaluation of an immunoassay for high-grade cervical pre-cancer screening among women presenting for colposcopy in Brazil

13. Screening methods

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Background / Objectives

Invasive cervical Cancer (ICC) affects women without sufficient access to care, with higher rates among minority groups in higher-income countries and women in low-resource regions of the world. Early diagnosis of high-grade cervicalintraepithelial neoplasia (CIN2/3) is vital for effective prevention of cervical cancer. Expression of the biomarkers P16INK4A and KRT7 has been associated with a higher risk of squamous intraepithelial lesions. The development of a highly sensitive and specific Point of Care (POC) screening test could dramatically increase access to screening for women with difficulties obtaining in-clinic cervical screening.

Our objective was to evaluate the expression of P16INK4A and KRT7 and assess the clinical performance of an investigational POC assay in an enriched population of women presenting for colposcopy following an abnormal cytologyresult.

Results

Women were enrolled if they were aged 25-50 years, not pregnant, and referred to colposcopy following an abnormal cytology test within the last 6 months. Women able and willing to give informed consent provided cervical specimens for testing by a new investigational POC test, and for an HPV test (Roche Cobas® HPV Test). Blood samples were also be taken for HIV serological testing. The expression of the biomarkers P16INK4A and KRT7 were evaluated using a particle-based sandwich immunoassay with the signal based on Surface Enhanced Raman Scattering (SERS). We specifically investigated the correlation between the investigational POC assay and the diagnostic test results collected during this trial (cytology, high-risk HPV status and histology/pathology). Receiver Operator Characteristic (ROC) curves

were generated using a Proper Binormal Model (PBM). Unique threshold levels were used for each assay in the multiplex. Optimal positive/negative cutoff values were determined by calculating the Youden Index Point.

Conclusion

To date, a total of 95 women participated, with a median age of 38 years and all of whom were HIV negative. The high-risk HPV DNA test showed HPV positivity in 60 (63%) of the subjects with 1 invalid result (1%). During the colposcopy, 64 patients had an indication of biopsy: squamous cell carcinoma (n=1), CIN3 (n=20) CIN2/3, (n=10) CIN2 (n=4), CIN1 (n=11) and normal (n=18). Considering the end point as CIN2+, P16INK4A sensitivity was 56.2% (95%CI: 40.9, 71.5) and specificity 86.5% (95%CI: 71.1, 97.8).The sensitivity and specificity of the P16INK4A/KRT7 ratio were 70.2% (95%CI: 55.3, 85.1) and specificity 81.8% (95%CI: 65.6, 94.3).

References

Conclusion: The P16INK4A biomarker provided the strongest correlation with the histopathology result. This Initial data also showed improved performance when the KRT7 biomarker is also considered in the algorithm.

14. Liquid based cytology

00253

THE EVALUATION OF p16/Ki-67 DUAL STAIN CYTOLOGY AS AN ADJUNCTIVE TOOL TRIAGING WOMEN WITH ASCUS AND LSIL CYTOLOGY

14. Liquid based cytology

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Background / Objectives

The detection of HGSIL (CIN2+) among women with ASCUS and LSIL cytology is challenging. The purpose of this study is to assess the diagnostic performance of p16/Ki-67 dual stain cytology and Hr-HPV test in women with ASCUS and LSIL cytological abnormalities.

Results

Consecutive liquid-based cytological samples (ThinPrep pap tests) were collected from 146 women diagnosed with ASCUS (n=67) and LSIL (n=77). Both, Hr-HPV test (HC2) and p16/Ki-67 dual stain immunochemistry (CINtec Plus test) were performed by the residual material of the vial of liquid-based cytology. Two cases were excluded from the study (2 ASCUS) due to inadequate material into the vial. All women were referred to colposcopy for the detection of CIN2+ lesions, with or without diagnostic biopsies.

Conclusion

Four cases of histologically confirmed HSIL were detected by the group of ASCUS diagnoses (prevalence rate 5.97%), as well as 18 cases of HSIL were also detected by the group of LSIL cytological abnormalities (prevalence 23.37%). Furthermore, in the LSIL study cases, 17 cases out of the 18 histologically confirmed CIN2+ were identified, by using the dual stain cytology (94.44%) comparable to 15 cases obtained by the HPV testing (88.23%). Finally, both dual staining and HPV testing

had the same results (4 to 4 cases) in predicting HSIL abnormalities, among women with ASCUS cytology.

References

The accuracy of dual staining was higher concerning the diagnosis of CIN2+, in women with LSIL (94.44%) comparable to HPV testing (88.28%). Nevertheless, additional studies would be conducted to further access of p16/Ki-67 dual stain cytology, as an adjunct tool to other tests, for improving the triage of LSIL cytology.

15. Automation in cytology

00419

Automated High-Throughput Cytology using Rapid Evaporative Ionization Mass Spectrometry (REIMS)

15. Automation in cytology

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Background / Objectives

Introduction: One in ten women screened for cervical changes will have an abnormal result. Cytological abnormalities can be difficult to manage and often require repeat visits with increased patient anxiety and risk of non-compliance. Furthermore, there is great variability in cytology reporting across cytotechnicians. Here, we investigate whether Rapid Evaporative Ionization Mass Spectrometry (REIMS) could be an automated alternative to assess the presence and grade of cytological abnormality at the bedside.

Results

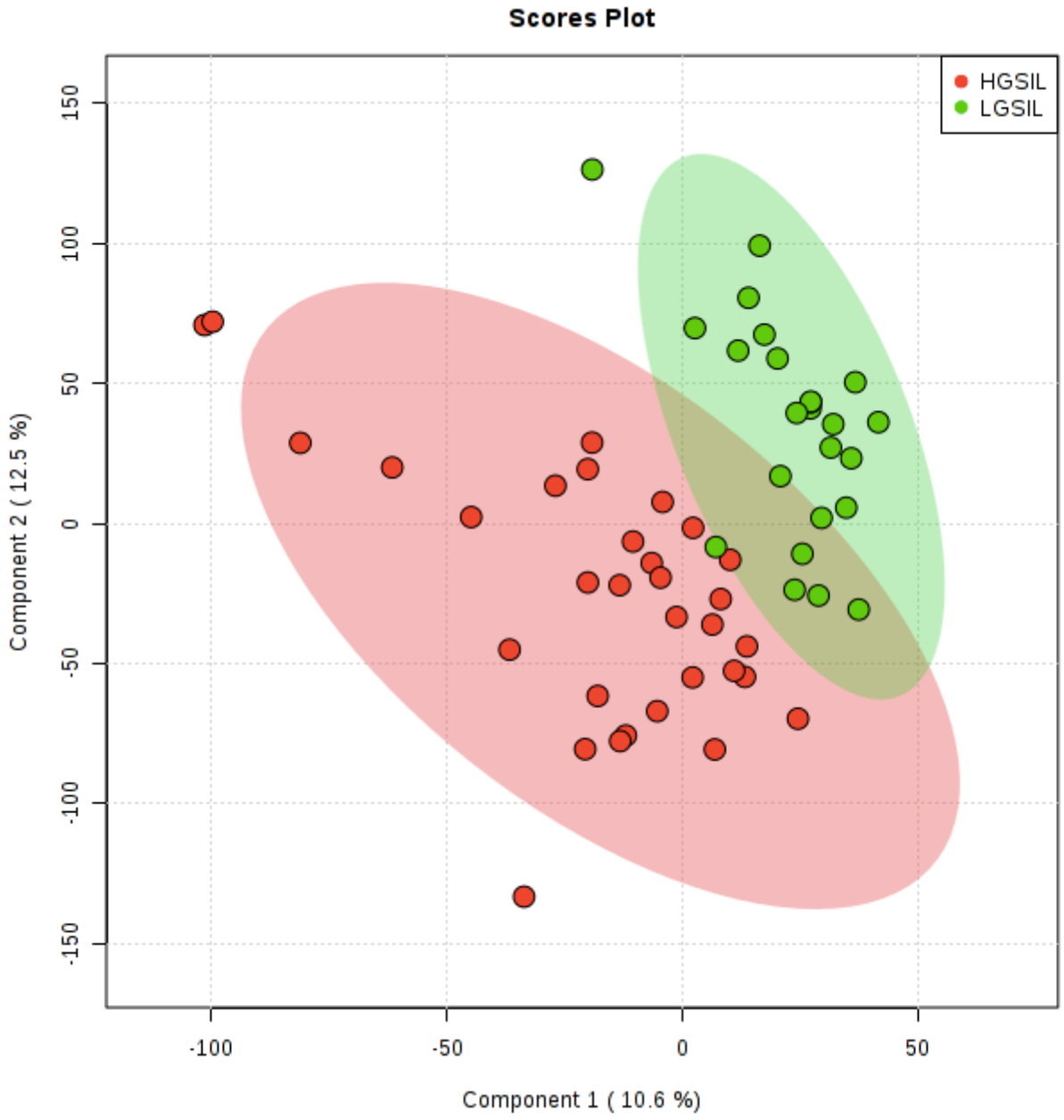
Material & Methods: We recruited women with cytological abnormalities and normal controls and collected a liquid based cytology (LBC) cervical smear. Prior to REIMS analysis, 2 mL of sample underwent centrifugation to pellet cells, which were then heated using a carbon dioxide laser and the generated aerosol aspirated to a mass spectrometer. The resulting mass spectra underwent standard processing, with multivariate statistics completed using MetaboAnalyst.

Conclusion

Results: A total of 94 LBC samples underwent the REIMS testing. 19 samples did not produce adequate spectra leaving 75 LBCs (four normal, 14 HPV changes only, 14 CIN1, 16 CIN2, 12 CIN3 and 15 cervical cancer) for analysis. Promising classification of LBC pellets by smear result using discriminant analysis was demonstrated - providing a platform for developing a classification model for larger cohorts. Further successful results included separation of samples positive and negative for HPV infection including a subanalysis of borderline/mild samples, classification of ‘normal/HPV changes/CIN 1 vs CIN2/3/cancer’, ‘HGSIL vs LGSIL’ and ‘normal vs LGSIL vs HGSIL vs cancer’.

References

Conclusion: This novel approach signifies an exciting step in translating laboratory-based diagnostics to the clinical setting as a bedside test with instant results. If the use of REIMS in cervical cytology proves to be as accurate in larger cohorts, this has the potential for use in the primary care setting as a rapid low-cost bedside screening tool for cervical cancer that could replace cervical cytology and/or a HPV DNA test.



16. Methylation

00449

Clinical performance of a quantitative specific methylation PCR test on a cohort of HPV positive women aged ≥ 30 years

16. Methylation

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Background / Objectives

HPV-based cervical cancer screening should be supported by efficient triage. In this study we evaluated efficacy of a quantitative multiplex methylation specific PCR, as a triage test in HPV positive women aged ≥ 30. The test is based on DNA methylation analysis of the host tumor suppressor genes *FAM19A4* and *miR124-2*, potential biomarkers for detection of progression of cervical cancer.

Results

Cervical specimens were obtained from the representative Slovenian population cohort attending national cytology-based cervical screening during 2009-2014. Cervical samples were collected in ThinPrep PreservCyt medium, aliquoted and tested for HPV using Hybrid Capture 2 (Qiagen) and RealTime High Risk HPV (Abbott). Cytology examination results were interpreted by certified cytologists who were blinded to HPV results. DNA from cervical specimens was extracted using QIAamp DNA Investigator Kit, BioRobot EZ1 or STARMag Cartridge Kit according to manufacturers' instructions. DNA with concentration above cut-off value of 0.8 ng/mL was bisulphite treated using EZ DNA Methylation Kit and the methylation of *FAM19A4* and *miR124-2* host cell genes determined using a quantitative multiplex methylation specific PCR (Qiagen) on Rotor-Gene Q MDx instrument.

Conclusion

A total of 950 samples obtained from HPV positive women aged ≥ 30 were included in the study. Overall methylation positivity rate was 28.3% (269/950) and was highest among women with HSIL (70.8%, 51/72) and ASC-H (60.0%, 3/5). Positivity rate according to histology was as follows: all samples obtained from women with invasive cancer were methylation positive (4/4), 79.2% (42/53) of women with CIN3 were positive, as well as 52.5% (21/40) women with CIN2, and 23.7% women with ≤ CIN1 lesions (202/853). Clinical sensitivity of the methylation test for CIN2+ was

69.1% (67/97; 95% confidence interval (CI), 58.9-78.1%) and clinical specificity 76.3% (651/853; 95% CI, 73.3-79.1%), while sensitivity and specificity for CIN3+ were 80.7% (46/57; 95% CI, 68.1-90.0%) and 75.0% (670/893; 95% CI, 72.1-77.8%), respectively.

References

The methylation PCR test used has shown good clinical sensitivity and specificity for CIN3+ lesions in population of women aged ≥ 30 and can be considered as possible triage test for HPV positive women.

00480

DNA Methylation Panel for the Triage of HPV Positive Women in a Primary Screening Population.

16. Methylation

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Background / Objectives

Triage of HPV positive women is one of the key challenges facing HPV primary screening. Specific triage tests to avoid large numbers of unnecessary referrals are required. Host methylation factors have been repeatedly shown to be hypermethylated in cervical cancer/pre-cancer and have the potential to triage HPV positive women at high risk of cervical cancer. This study aims to investigate methylation of a specific panel of three markers [CADM1-M18, MALM1 and hsa-mir124-2] in HPV positive women. This study is part of a larger CERVIVA HPV Primary Screening Study.

Results

In partnership with CervicalCheck, The National Cervical Screening Programme in Ireland, CERVIVA are undertaking a longitudinal HPV primary screening pilot study evaluating triage strategies for managing HPV-positive primary screening tests. In total, 13,496 women attending for routine screening have been enrolled. HPV testing is performed using the Cobas HPV DNA test. HPV positive samples are tested for a panel of methylation specific biomarkers [CADM1-M18, MAL-M1, hsa-mir-124-2] via Quantitative Methylation-specific PCR. Here we present the pre-validation and optimisation work for the Methylation Panel for the use in a HPV Primary Screening Population.

Conclusion

Initial optimisation of the qMSP was carried out on methylation positive SiHa cells and HPV negative/cytology no abnormality detected (NAD) smear samples. The SiHa cells showed detectable qMSP product for all markers and NAD samples remained undetected through qMSP. Serially diluted bisulfite converted SiHa DNA showed detectable methylation of at least 500pg/µl and no greater than 5pg/µl. To show that methylation is raised in high grade cervical lesions a small cohort of smears with CIN3 follow up histology (n=15), HPV negative cytology NAD (n=15) and HPV positive cytology NAD (n=15) were tested for the CAD M1-M18, MAL M1 and hsa-mir-124-2. CIN3 samples showed detectable qMSP product compared to both HPV negative/NAD and HPV positive/NAD samples (p=0.082, 0.045, 0.016 & p=0.083, 0.044, 0.016). Use of a Total Methylation Score (CAD+MAL+mir) showed statistically significant values (p=0.033 for both).

References

From our research the use of CADM1-M18, MAL-M1 and hsa-mir-124-2 in a primary screening population is feasible. The approximate LOD of methylated DNA in a qMSP is <70 methylated cells and the small cohort of CIN3 samples showed significant differences when compared to normal controls. The use of a Total Methylation Score also shows promise in aiding differentiation of high grade, relevant lesions from normal cervical smears and hopefully provide a more stable and understandable result for scientists and clinicians if adopted into the National Screening Programme. A larger validation panel is set to determine the utility of this methylation panel.

19. New technologies

00141

Comparison of visual and cytology cervical cancer screening in Maharashtra, India

19. New technologies

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Background / Objectives

Objective: To assess the concordance between EVA and Pap in an Indian clinic. **Background**: India has the most deaths from cervical cancer in the world. When available, cytology is the primary method of screening for cervical cancer. Because cytology requires a laboratory infrastructure, visual screening - digital cervicography using a smartphone-based colposcope (Enhanced Visual Assessment (EVA) System) - was proposed. In this study, visual screening using the EVA System is compared to cytology.

Results

Altogether, N=327 women, 20-50 years old from the Mumbai region of India were enrolled in the study. XXX patients enrolled in Hirnandani Hospital, YYY patients enrolled in screening camps. Patients were screened using both the EVA System and cytology. Patients positive with either method were referred to colposcopy with biopsy, following the standard of care.

Conclusion

Of the N=327 patients, 304 patients were EVA-/Pap-, 19 patients were EVA+/Pap-, 0 Patients were EVA-/Pap+, and 4 patients were EVA+/Pap+. The Pap+ rate (1.2%) appears to be much lower than one would expect in India; the EVA+ rate (7.0%) is more believable. Of the 16 biopsies in total, 8 were positive. Of these 8 positive biopsies, 5 were EVA+, only 1 was Pap+. Although the sample size is very low, these results suggest cytology is missing many positive patients (7 of 8). In comparison, EVA caught most of the positive patients (5 of 8).

References

These results suggest that cytology screening results had false negatives, some of which were caught by the EVA System. Feasibility of visual cervical cancer screening with a mobile colposcope was demonstrated. Additional research is needed to find a way to mitigate the frequency of loss to follow up, which was significant in this study.

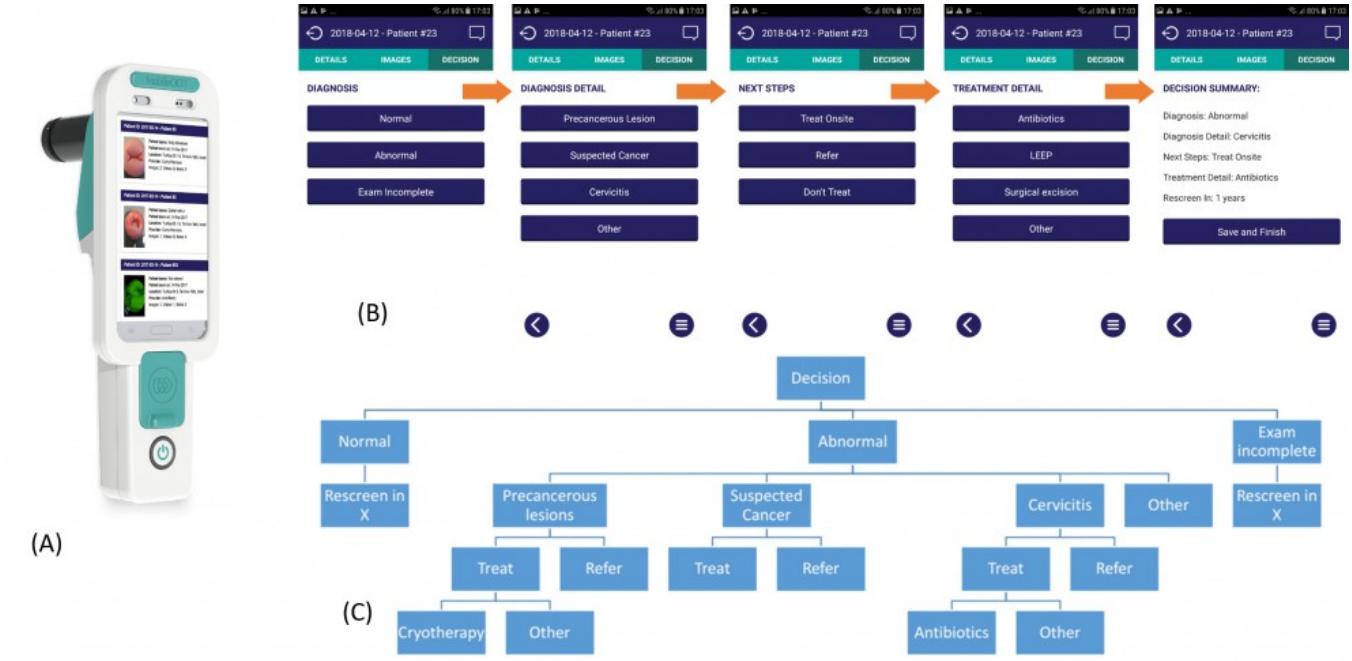

Fig. 1: (A) EVA System. (B) Screenshots of Decision Support Job Aid on the EVA System app. (C) Full decision tree of job aid.

00269

A NOVEL APPROACH TO IDENTIFY PROTEINS BY GEL-BASED PROTEOMICS IN RESIDUAL CERVICAL CYTOLOGY SAMPLES DURING CERVICAL CARCINOGENESIS

19. New technologies

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Background / Objectives

The introduction of HPV-DNA test improved the effectiveness of Cervical Cancer (CC) Screening Programs, but its high sensitivity frequently leads to unnecessary follow-up and over-treatments [1]. Besides unregulated HPV E6/E7 genes expression represents a key event, other factors seem to be implicated in the progression of HPV-related lesions. Proteomics is a growing technology for the study of proteome. An omic sentence says "The study of proteome is useful to identify novel biomarkers. If genome carrying the genetic information suggests what can happen, only the proteins, being the final workers of life events, indicates what makes it really happen". Thus, to screen for proteins expression during cervical cancerogenesis would signify to better understand and predict which mechanisms triggered by HPV are able to drive cells toward cancer.

In this retrospective study we firstly assessed the feasibility of residual cytological samples stored in PreservCyt medium (Hologic, USA) for 2D gel-based proteomics combined with MALDI-TOF Mass Spectrometry. Then, we compared proteome from specimens showing different diagnosis regarding HPV infection.

Results

In our Institution is placed a Tissue and Cell Biobank (Adriatic Biobank) holding about 50,000 residual PreservCyt specimens collected from women participating in the Regional Cervical Cancer Screening Program. For our purposes, we retrieved 12 samples related to patients grouped as follows: HPV-negative (reference negative group), HPV-DNA positive/E6-E7 negative (+/-), HPV-DNA positive/E6-E7 positive (+/+), CC. A 5 mL aliquot from each sample was removed to evaluate proteins yield

using the Coomassie protein assay (Better Bradford Pierce, USA). Then we proceeded with 2-DE analyses, combined with MALDI-TOF MS/MS. All samples were electrophoretically run three times as technical and biological replicates.

Conclusion

We estimated an average total protein content of about 1.5 mg. For each biological replicated, 2DE resolved a total number of 745 ±115 protein spots. Comparison of all 2D maps demonstrated different protein profilings. In particular, when compared with negative group, a low matching percentage of 47 and 37 were detected in +/+ and carcinoma groups, respectively. Gene Ontology analysis (Panther) classifies the MS/MS assigned proteins in biological categories as follows: protein biosynthesis, cellular transport and immunity.

References

Residual methanol-based cytological specimens are suitable for proteomic analysis. Proteomics demonstrated to be precious to selectively target differences in proteins expression during the different steps of cervical carcinogenesis [2,3].

References

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00489

EVALUATION OF A NOVEL ISOTHERMAL AMPLIFICATION ASSAY FOR RAPID HPV DNA DETECTION AND GENOTYPING

19. New technologies

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Background / Objectives

Methods to determine human papillomavirus (HPV) genotypes, especially of HPV16 and HPV18, are regarded as useful for the prevention of cervical cancer. A large number of assays designed for HPV genotyping have been developed in recent decades. They have variable analytical sensitivity and specificity for different HPV genotypes and may be used for routine clinical diagnosis, epidemiological studies, and evaluation of vaccine efficacy and monitoring. The objective of our study was to assess the performance of the new AmpFire HPV assay, comparing it to results obtained by other HPV genotyping tests, including from Roche, Becton Dickinson, Abbott, and InnoGenetics.

Results

AmpFire HPV detection technology (Atila BioSystems) is an isothermal amplification assay, with a simple sample processing protocol. The test can detect fifteen high risk HPV types in a single tube reaction and also genotype HPV16 and HPV18 using real-time fluorescent detection. The assay does not require extraction of DNA. Raw samples are heated and lysed prior to isothermal amplification. The new HPV test can be completed within an hour, including hands-on time. Eight samples were chosen for repeat testing and dilutions of 1:5 and 1:50. HPV16 plasmid DNA was diluted to assess assay analytical sensitivity. 60 fresh samples stored in PreservCyt medium were tested with the cocktail HPV assay; 45 samples with multiple infections (HPV16, HPV18, plus other types) were analyzed with the genotyping assay. An additional 20 archived samples (stored in PreservCyt at -20C for 10+ years) were also tested.

Conclusion

AmpFire had excellent reproducibility (>95%), with an analytical sensitivity of less than 10 copies of HPV16 DNA and worked well on 1:50 dilutions of clinical samples. On the fresh samples we observed almost identical results to commercial tests (Abbott n=60, 98% agreement; InnoGenetics SPF10 n=58, 97% agreement). We also compared the performance of AmpFire genotyping results to SPF10-LiPA25 in 45 samples with multiple HPV types. 44.4% showed identical results and 33.3% showed partial agreement. Overall, the two assays mostly agreed with each other. We tested 20 samples archived in PreservCyt for more than ten years, comparing our results to the original data on the Abbott, Roche and, Becton Dickinson tests. Seventeen of 20 samples showed identical results between AmpFire and the other HPV tests.

References

The AmpFire assay is promising as a new routine HPV DNA detection and genotyping test. It has an isothermal microplate-based format and features minimal instrumentation and a rapid simple procedure that can produce accurate results in about one hour.

00584

HUMAN UTERINE CERVIX-ON-A-CHIP: ESTABLISHING THE FIRST IN VITRO MODEL TO STUDY THE DEVELOPMENT OF CERVICAL CARCINOMA AND HUMAN PAPILOMA VIRUS MECHANISM OF ACTION

19. New technologies

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Background / Objectives

Predicting the effects of drugs before human clinical trials is at the heart of drug screening and discovery processes. The cost of drug discovery is steadily increasing owing to the limited predictability of two-dimensional (2D) cell culture and animal models. The conjunction of microfabrication and tissue engineering led to organ-on-a-chip technologies, which offer an alternative to conventional preclinical models for drug screening. Organ-on-a-chip devices can imitate key aspects of human physiology fundamental for the understanding of drug effects, improving preclinical safety and efficacy testing. This technique recently allowed creating microfluidic chips that can partially mimic organ function such as liver, lungs, gut and even tumors on chip.

The objective of this study was to develop a microfluidic ‘uterine cervix-on-a-chip’ platform that let the cultured cells to take characteristic positions similar to those observed in native human uterine cervix. This platform would be able to be used as an in vitro model to study the transformation zone of cervix during Human Papilloma virus (HPV) infection and cervical cancer developing (figure 1).

Results

A microfluidic device prepared by demolding cured polidimetilsiloxano (PDMS). On the chip, we carried out cell culture and co-culture of ectocervical epithelial cells (Ect1/E6E7) and endocervical epithelial cells (End1/E6E7) cell lines. Endocervix epithelial cell has been marked by AAV-GFP control viruses to provide a convenient

way to measure transduction efficiency into endocervix cells via fluorescence and to differentiate them from ectocervix epithelial cells. Numbers of experiments have been designed to check the functionality of the chip, such as live/dead assay, prestoBlue cell viability, 2D migration of cells (scratch tests) and 3D migration of cells by the use of 3D printers.

Conclusion

We found that both cell lines can grow from both sides of the chip to reach each other in order to make the transformation zone and prepare the squamo-columnar junction. This multilayer-cell junction contains both types of epithelial cells and can mimic the transformation zone of cervix practically.

References

Uterine cervix-on-a-chip may provide a powerful alternative in vitro model for studies on uterine physiology, real-time, high-resolution imaging, and analysis of biological responses in the cervix, as well as drug development. This established uterine cervix-on-a-chip is simple, effective, and easy to operate. It is expected to have important applications in personalized treatment of HPV infection lesions and cervical cancer and to play a potential role in other clinical treatments and tissue engineering.

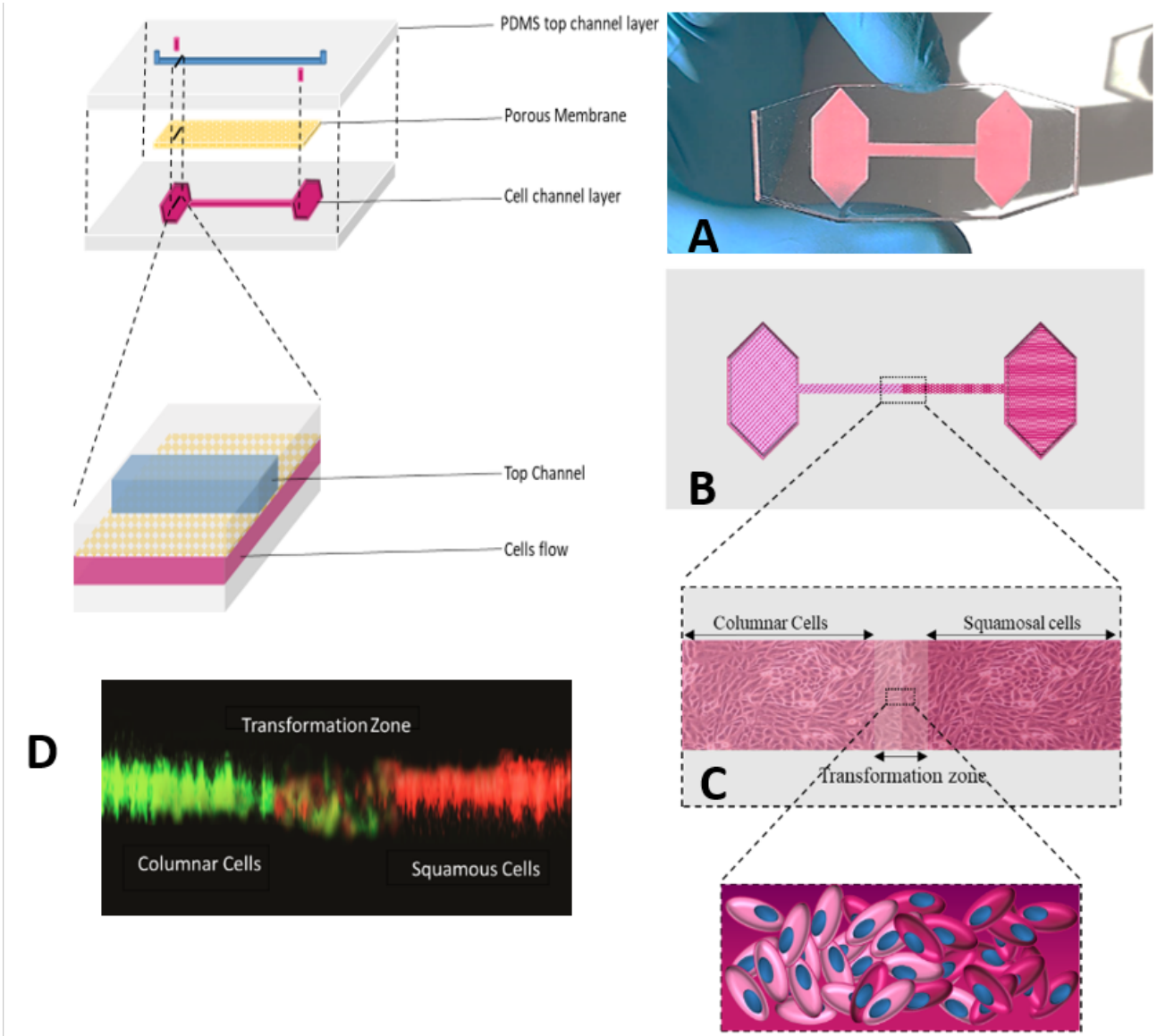

Figure 1. Illustration showing the distribution of epithelia of the ectocervix (dark pink) and endocervix cells (pale pink). (A, B, C) Lower cell layer of the chip. (D) Two PDMS layers are aligned and irreversibly bonded to form two sets of parallel microchannels separated by a 22-µm-thick polycarbonate membranes, containing an array of through-holes with an effective diameter of 22-µm. Scale bar, 200 µm. (E) Long-term microfluidic co-culture produces a tissue-tissue interface consisting of a single layer of the Columnar epithelium (stained with Cell Tracker Green) closely next to a monolayer of the Squamous epithelium (stained with Cell Tracker Red), both of which express intercellular junctional structures stained with antibodies to VE-cadherin. Scale bar, 50 µm.

20. Diagnostic procedures / management

00126

CYTOMORPHOLOGICAL PARALLELS OF PATOLOGY OF GLANDULAR EPITHELIUM OF CERVIX AMONG REPRODUCTIVE AGE WOMEN

20. Diagnostic procedures / management

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Background / Objectives

The incidence of glandular cervical cancer has increased in Western countries from 5 to 25% of all cases of malignant neoplasms of the cervix. Cytological and histological criteria of cervical adenocarcinoma are developed much later than squamous cell carcinoma, in addition, the study material obtained from the cervical canal is often less informative.

Results

The results of cytology and cervical scraping of 86 women with different pathology of glandular epithelium were analyzed. Mean age was 32.1±8.4.

Conclusion

Among 58 patients were found signs of chronic inflammation of different degree of severity and variable in activity of inflammation. 2 patients had chronic follicular cervicitis. The data were obtained from morphological and cytological investigation. 26 patients of inflammatory infiltrates were not detected in traditional or liquid cytology, histological examination revealed scanty lymphohystiocytic infiltrates in the submucosal layer. In 49 cases we detected signs of endocervical glandular hyperplasia, 2 endometrioid heterotopia, 27 reactive glandular changes, in 7 AGC and 1 AIS confirmed by immunohistochemistry (Ki67, CEA, p16). In traditional cytology, evaluation of the condition of the glandular epithelium was somewhat difficult due to application of the material (in 28 the glandular epithelium of 86 traditional smears was not visible due to thickness and presence of erythrocytes), in liquid cytology the glandular cells in the structures are well cytological signs of hyperplasia, atypia, reactive changes were noted (in 6 it was not possible to evaluate glandular epithelium due to high density of location of glandular structures). Hyperplasia of glandular epithelium of cervix was represented mainly by micro-glandular hyperplasia of endocervix, microparapillary formations, in some cases with

foci of squamous metaplasia, glandular and glandular-cystic hyperplasia. In 1 case intestinal metaplasia was detected and confirmed by additional stains for mucin. Reactive changes are a fairly common group of various changes in glandular epithelium, including atypia, as a result of inflammation. These changes were also found in cytological and morphological material in 35 cases. In cytological study, the degree of change was more pronounced, which provoked the overdiagnosis of atypical changes (in 16). In morphological study of biopsy the presence of a massive inflammatory infiltrate in stroma and more relaxed histological pattern in the glandular epithelium allowed to reduce the degree of severity of pathological process in morphological conclusion.

References

A comprehensive study of cervical problem will increase level of early detection and reduce incidence in women of reproductive period.

00220

COLPOSCOPIC AND HISTOLOGICAL FINDINGS IN WOMEN WITH LOW GRADE INTRAEPITHELIAL LESION (LSIL) SUBMITTED TO ZT EXCISION

20. Diagnostic procedures / management

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Background / Objectives

Low-grade intraepithelial lesions occur at 2.9% of cervical cytologies and are usually associated to HPV cellular changes and mild dysplasia that can regress with no treatment. It is a cytological finding that carries a risk of 25% to high-grade development within 2 years.

The aim of this study is to correlate the colposcopic and histological findings in women with LSIL cytology.

Results

We conducted an observational, descriptive, retrospective study. The sample included all women with LSIL cytology who were submitted to ZT excision, during their follow up at cervical pathology unit of Centro Hospitalar e Universitário do Algarve – Unidade de Faro, between 2012- 2016. The data was analysed with SPSS 21.

Conclusion

From the 572 women with LSIL cytology referred to our cervical pathology unit, we studied 125 women (21,85%) that were submitted to ZT excision during their follow up. The mean age of the women was 39 years old (range 24 to 66 years old). The mean age of first sexual intercourse was 17 years old and the mean number of sexual partners was 4. 12,5% of the women were postmenopausal. About 56% had smoking habits and only 4% had HPV vaccination.

We found that 60% of the women presented grade 2 and 35% grade 1 colposcopic findings. Only 5% had normal colposcopy. 84% of the lesions visualized at colposcopy examination were biopsied and 64,8% of them revealed high-grade

lesions. The pathology exam of ZT excision revealed 53,6% HSIL, 34,4% LSIL and 11,2% no alterations. Women with grade 1 colposcopy findings had high-grade lesions in 54,8% of the cases. Only 27,8% of the women with grade 2 findings revealed a ZT excision without lesion or with a low-grade lesion.

References

LSIL cytology is associated with transitory HPV infection, however sometimes they can have underlying high-grade lesions. In the present study we verified that the rate of high-grade lesions at ZT excision was 53,6%, showing that women with LSIL cytology must have surveillance with HPV test and colposcopy. These women follow-up is essential and the decision between treatment and an expectant approach should consider the concordance between results of cytology, HPV test, colposcopy, biopsy, age and parity.

00265

HUMAN PAPILLOMA VIRUS IN URINE AND BLADDER CANCER RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS.

20. Diagnostic procedures / management

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Background / Objectives

Association between human papilloma virus (HPV) infection and risk of bladder cancer (BlCa) remain inconclusive. We carried out a systematic review with meta-analysis of the available case-control studies in order to verify possible differences in the occurrence of HPV infection in urine samples in patients with BlCa and and normal subjects.

Results

PubMed was used to search for articles published from January 1965 to August 2018 using the key words "bladder cancer" and "HPV". No restrictions to date, language, or article type were applied. Case-control studies reporting Odds Ratio (OR) for HPV infection in urine samples in patients with BlCa and and normal subjects were analyzed. The quality of the studies was evaluated by the New Castle Ottawa scale. Data were combined using random effect models. The Cochrane Chi-square (Cochrane Q) statistic and the I-square test were used to analyze heterogeneity. The publication bias was graphically explored through funnel plot, and Duval and Tweedie's "trim-and-fill" test was used to correct possible publication bias.

Conclusion

The selection process yielded only three studies with eligibly criteria for analysis, that gave information on 278 patients with HPV infection in urine and 903 patients without HPV infection in urine. The pooled OR estimated showed that patients with HPV infection in urine exhibit a significantly higher prevalence in BlCa than patients without HPV infection (OR = 2.602, 95%CI: 1.484, 4.56; P = 0.001). We obtained a heterogeneity chi-squared value Q exp=1.573 (p=0.456) (I-square = 0%) . Funnel

plot non suggested a possible publication bias in the analysis.Only one study compared the incidence of HPV infection in urine with HPV infection at the tissue level. A higher incidence of HPV infection was observed in the urine of patients with bladder cancer than in tumor tissue.

References

The pooled OR value showed a moderate relationship between urinary HPV infection and BlCa. HPV infection in the urine may have a role in carcinogenesis of the bladder tumor. Further well-conducted studies could be useful to confirm this conclusion, and thus be able to identify if the determination of HPV in urine can be considered useful in clinical practice for its use in the diagnosis and follow-up of patients with BlCa.

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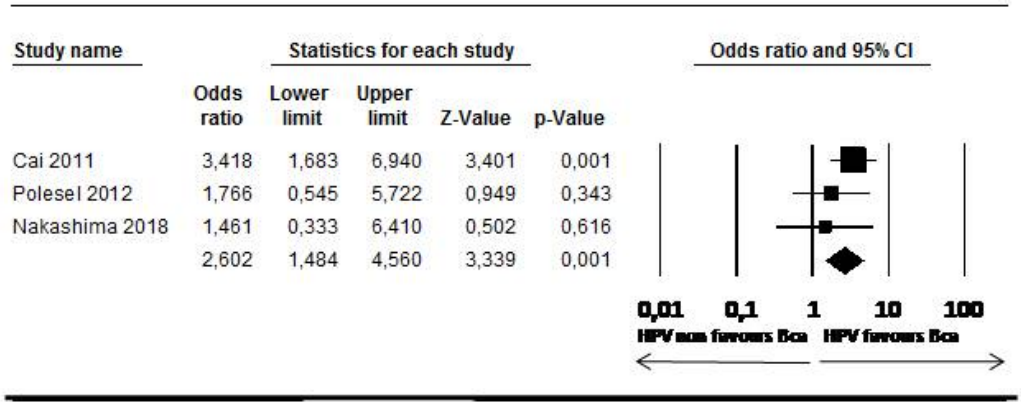
Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Z-Value
p-Value
Cai 2011 3,418 1,683 6,940 3,401 0,001
Polesel 2012 1,766 0,545 5,722 0,949 0,343
Nakashima 2018 1,461 0,333 6,410 0,502 0,616
2,602 1,484 4,560 3,339 0,001
0,01
0,1
1
10
100
HPV non favours Bca
HPV favours Bca
Meta Analysis

00428

COMPARATIVE PERFORMANCE OF HPV DNA AND MESSENGER RNA TESTS IN THE POST-LEEP TEST-OF-CURE SETTING

20. Diagnostic procedures / management

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Background / Objectives

In British Columbia (BC), women undergoing loop electrosurgical excision procedure (LEEP) for CIN2+ are tested approximately 6 months post-LEEP with the hybrid capture 2 HPV DNA test (HC2). Women HC2 negative with negative histopathology are discharged to routine screening, while those HC2 positive continue follow-up within the provincial colposcopy program. Since various HPV screening tests may have different performance characteristics in the test-of-cure setting, our objective was to evaluate the performance of other HPV DNA and mRNA tests compared to the standard of care (HC2).

Results

Three hundred one (301) women attending their first post-LEEP visit were enrolled from December 2016-May 2017 and were tested by HC2. Follow-up management was based on HC2 results and histopathology findings. Residual post-LEEP samples were then tested by the cobas 4800 HPV DNA test (Roche), RealTime High Risk HPV DNA test (Abbott) and the Aptima HPV mRNA assay (Hologic). Overall, positive and negative agreement with HC2 were calculated. All CIN outcomes following the post-LEEP HC2 test were obtained from the centralized BC cervix screening program database.

Conclusion

Valid results were obtained for 301 samples with the HC2, cobas and Aptima tests, while the RealTime test had three invalid results (HPV negative by all the other tests). Percent positive was 30.6% (91/301) for HC2, 29.6% (89/301) for cobas,

31.5% (94/298) for RealTime and 23.6% (71/301) for Aptima. Overall, positive and negative agreement is shown in the Table. Agreement between HPV DNA tests was higher than for all DNA tests vs. Aptima. Analysis of CIN outcomes by HPV test result is in progress.

Summary of Agreement between HPV Tests

	Overall Agreement (95%CI)	Positive Agreement (95%CI)	Negative Agreement (95%CI)
HPV DNA vs. DNA			
HC2 vs. cobas	96.7% (94.0-98.2)	88.4% (82.9-92.3)	95.0% (92.5-96.7)
HC2 vs. RealTime	94.6% (91.5-96.7)	91.4% (86.5-94.6)	96.1% (93.8-97.6)
cobas vs. RealTime	94.3% (91.1-96.4)	90.7% (85.6-94.1)	96.1% (93.8-97.6)
HPV DNA vs. mRNA			
HC2 vs. Aptima	90.4% (86.5-93.2)	82.2% (75.6-87.3)	93.4% (90.7-95.4)
cobas vs. Aptima	87.4% (83.2-90.7)	76.3% (69.1-82.2)	91.4% (88.4-93.7)
RealTime vs. Aptima	87.6% (83.4-90.9)	77.6% (70.6-83.3)	91.4% (88.4-93.7)

References

The HPV DNA tests all had similar performance vs. the other DNA tests. All DNA tests had lower agreement with Aptima, primarily due to the smaller number of positive Aptima tests. If Aptima is shown to detect statistically similar rates of residual CIN2+ disease compared to the DNA tests, it would increase the number of women returned to routine screening vs. extended follow-up within the colposcopy program.

00437

CONNECTION BETWEEN THE FREQUENCY OF PREVENTIVE GYNECOLOGICAL EXAMINATIONS AND CERVICAL CANCER DETECTION: A CASE-CONTROL STUDY

20. Diagnostic procedures / management

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Background / Objectives

The task of organized screening of cervical cancer has not been solved in Russia currently. In practice, the examination of patients to identify cervical disease includes isolated or combined use of the following methods: gynecological examination, colposcopy, cytology and HPV tests. The aim of our study was to establish a connection between the frequency of preventive gynecological examinations and detection of cervical cancer.

Results

The study included 115 patients with diagnosis of cervical cancer at various stages of the pathological process: Cr in situ – 13.0%; IA1 – 13.9%; IA2 – 3.5%; IB1 – 35.7%; IB2 – 2.6%, IIA – 12.2%; IIB – 7.0%; IIIB – 3.5%; IV – 1.7%; without an exact stage – 7.0%. The average age of diagnosis was 42.6 years. According to the medical documentation, data was received on the passage of preventive examinations at the gynecologist and screening for cervical cancer in the last 5 years before the diagnosis was established.

Conclusion

Patients who visited the gynecologist more than once a year, in the majority had concomitant pathology from the side of the reproductive system, which caused an increased frequency of gynecological examinations. Among those who did not undergo screening for cervical cancer or who had undergone it on detection of the disease, the risk of diagnosing in stage II-IV was 5.2 times higher than among those who underwent

cervical screening two years ago, or once a year in over the past five years (OR=5.2; 95% CI: 1.1–24.5).

References

The current opportunistic nature of screening for cervical cancer in Russia can not lead to a significant reduction in morbidity. It is necessary to ensure the regularity and frequency of preventive examinations.

00458

HSIL MANAGEMENT IN YOUNG WOMEN

20. Diagnostic procedures / management

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Hospital Prof. Doutor Fernando Fonseca - Amadora (Portugal)

Background / Objectives

Human papilloma virus (HPV) infection is most common in teenagers and women in their early 20s. Most young women have an effective immune response that, on average, clears the virus within the first 8 months. With the regression of the infection, most cervical neoplasia will spontaneously resolve in this population.

Although the risk of invasive cervical cancer in women with a finding of high-grade squamous intraepithelial lesion (HSIL) is substantial, HSIL are among the least common cytological findings. Younger women, under the age of 25, with HSIL have lower risk of invasive cervical cancer when compared with women at least 25 years old. For these reasons, and considering the risk of obstetric complications after cervical conization, observational management is recommended in this population, with adequate colposcopy and cytology every 6 months for 24 months. Persistence of CIN 2 or 3 over 24 months requires excisional treatment.

The primary objective of this study is to document the outcome of women under 25 years-old with HSIL managed in our colposcopy unit.

Results

Retrospective study of the cases of HSIL in women under 25 years-old managed in Hospital Prof. Doutor Fernando Fonseca (HFF) between January 2013 and December 2017. Data analyses – Microsoft® Excel version 2010

References

HSIL is an uncommon cytological finding particularly in young women. Observational management was preferred in cases of CIN 2 or lower anomalies as recommended in the literature, with favorable outcomes.

00469

VALUES OF HPV STATUS, SAMPLE MARGINS, AND ENDOCERVICAL CURETTEMENT AFTER LLETZ CONIZATION AS PROGNOSTIC FACTORS FOR SUCCESSFUL TREATMENT

20. Diagnostic procedures / management

D. Butorac [1], I. Stojanovic [2], M. Cukelj [2], N. Tuckar [2], A. Vukovic [2], S. Radovic Radovcic [2], I. Pitner [2], A. Šemper Majdandžic [3], K. Kuna [4]

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Background / Objectives

Control Pap smear test and HPV typization were performed six months after LLETZ conization as a part of continuous monitoring of patients who underwent LLETZ treatment. Pre-treatment HPV status, cone margins status, and endocervical curettement of the residual cervical canal were used as prognostic factors of success of the treatment of cervical intraepithelial lesions with LLETZ conization.

Results

The study included 34 female patients treated at Sestre Milosrdnice University Hospital Centre in 2017. In all patients LLETZ conization was performed. Patients were grouped according to Pap smear test and HPV typization six months after LLETZ conization.

Conclusion

The patient mean age was 43.32 years; there were 13 women (38.24%) in 27-39 age group, and 21 women (61.76%) in 40-68 age group. The first group was made up of 22 women (64.71%) whose Pap smear tests, performed six months after the treatment, were normal, and whose HPV typization was negative. Within this group 20 women (90.91%) had positive pre-conization HPV tests, and in two women

(9.09%) HPV tests were negative. HPV types 16 and 18 were confirmed in 10 women in this group (50%) whose HPV tests were positive. Positive margins were identified in five women (22.73%). Endocervical curettement was negative in all women in this group. In the second group abnormal Pap smear tests and/or positive HPV statuses were identified in 12 women (35.29%) six months post-conization. Prior to the treatment 11 women (91.67%) were HPV positive, whereby types 16 and 18 were present in 50% of women. Within this group margins were positive in 8 women (66.67%). In two women (16.67%) positive endocervical margins were detected, as well as a positive endocervical curettage, HSIL changes in the Pap smear test, and positive HPV status six months after the treatment. Positive HPV status six months after the treatment was confirmed in 9 women (75%) within this group. A Pap smear test performed six months after the treatment showed abnormalities in 6 women (50%) within this group; in three HSIL changes were observed.

References

The status of cone margins is the best prognostic factor for successful LLETZ treatment. We have to note that we have excluded multi-LLETZ treatments which would significantly increase the representation of positive margins. Its prognostic value increases with a positive test result of endocervical curettage and the residual HPV infection.

21. Colposcopy

00502

The accuracy of colposcopy utilizing RCI or Swede score combined with adjunct hrHPV for prediction of high-grade intraepithelial neoplasia (CIN2+) in the patients with ASC-US, ASC-H, LSIL and HSIL Pap smears on Bethesda classification

21. Colposcopy

P. Zubor [1], E.I. Mamen [1], E. Kudela [1], M. Nachajova [1], P. Slavik [2], M. Kalman [2], T. Bielik [1], I. Stastny [1], J. Danko [1]

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Background / Objectives

To determine the prevalence of cervical intraepithelial neoplasia CIN2+ (high-grade) among women with all spectra of squamous lesions on Bethesda classification. The assessment of colposcopy (Reid index and Swede score) with adjunct hrHPV test to predict CIN2+.

Results

A retrospective medical record review of 150 women attending colposcopic examination at the Clinic of Obstetrics and Gynaecology JMF CU in Martin in 2016. A reason for expert colposcopic evaluation was abnormal screening result on Bethesda classification. All women underwent colposcopy and the findings were scored by both Reid colposcopic index (RCI) and Swede score, biopsy was taken from all abnormal areas and adjunct HPV test was either conducted or reviewed from previous test done not more than 3 months prior expert colposcopy.

Conclusion

A 139 of initially enrolled 150 patients were reviewed based on all required entry data. Women aged 20 to 62 (mean 37.8 yrs.) were divided into subgroups accordingly smear results: AGC NOS (n=7), ASC-US (n=30), ASC-H (n=13), LSIL (n=64) and HSIL (n=25). Only squamous lesions have been evaluated in this study. A total of 40 (30.3%) CIN2+ lesions were detected. Prevalence of high-grade lesions

in women with ASC-US, ASC-H, LSIL and HSIL was 13.3% (4/30), 30.8% (4/13), 25.0% (16/64) and 64.0% (16/25), respectively. Reid colposcopic index at a cut-off of 2 showed sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for detection of CIN2+ lesions of 84.6%, 77.6%, 3.75 and 0.2 (AUC=0.863, p<0.0001). Using Swede score at a cut-off of 2 were data as follows: sensitivity 84.6%, specificity 72.6%, +LR 3.79, -LR 0.2 (AUC=0.822, p<0.0001). There was a significant correlation between RCI and histology ($\acute{r}$=0.5932, p<0.0001), as well as for Swede score ($\acute{r}$=0.5924, p<0.0001).

References

The expert colposcopy utilizing either Reid colposcopic index or Swede score with adjunct hrHPV test can be used flexibly depending on the setting and have high clinical diagnostic value for the detection of CIN2+ lesions. The lower threshold scores can be used for screening and higher for screen-and-treat selection to decrease the over/under-treatment rate.

00506

PRACTICE OF COLOPOSCOPY AT THE GYNECOLOGICAL AND OBSTETRICAL CLINIC OF CHU ARISTIDE DANTEC OF DAKAR (SENEGAL) FROM 2005 TO 2017 (SENEGAL): ABOUT 1559 CASES.

21. Colposcopy

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Cheikh Anta DIOP University, Obstetrics and Gynecology Clinics Aristide Le Dantec Hospital, Dakar, SénégalniversityObstetrics and Gynecology Clinics Aristide Le Dantec Hospital, Dakar, Sénégal - Dakar (Senegal)

Background / Objectives

OBJECTIVE: To specify the indications, the colposcopic and therapeutic aspects of the patients received at the Cervico-Vaginal Colposcopy and Pathology Unit of the Dantec Hospital for cervical cytological lesions according to the Bethesda classification.

Results

MATERIALS AND METHODS: This was a retrospective and descriptive study ranging from January 31, 2005 to January 31, 2017. All patients with pathological smear were included in the study. The studied parameters concerned epidemiological data, indications, colposcopic aspects, the results of the colposcopy biopsy in case of lesion, the therapeutic aspects, the results of the histology of the operative specimen and the follow-up. The collection was carried out thanks to the data collection sheet and the colposcopy register. The analysis was done by Epi version info 3.5.

Conclusion

RESULTS: During the study period, we performed 1559 colposcopies. Women in active periods predominated (67.5%) followed by menopausal women (24.5%). The mean age at first intercourse was 20.4 years with extremes of 10 and 46 years. The

mean gestational age was 4.9 with extremes of 0 and 19 and mean parity of 4.4 with extremes of 1 and 13. Patients used contraceptive products in 44.4% of cases. Indications for colposcopy were dominated by low-grade lesions (41.5%) followed by squamous cell abnormalities of indeterminate significance (14.9%). Colposcopy resulted in atypical Grade 2 transformation in 22.7%, atypical Grade 1 transformation in 19.6%. After 367 biopsies under colposcopy, the histology found a micro-invasive squamous cell carcinoma in 4.6%, a CIN 3 in 6.5%, a CIN 2 in 8.4%, a CIN 1 in 16.3%, and squamous metaplasia in 39.8%.
We performed 49 conizations and 42 hysterectomies. The postoperative course was simple in all our patients.
After surgical treatment, pathology examination showed CIN3 in 34% of cases, CIN2 in 22% of cases, CIN1 in 11% of cases, microinvasive squamous cell carcinoma in 17% of cases and was normal. in 17% of cases.

References

CONCLUSION: Colposcopy plays a key role in the management of cervical dysplasia

Keywords: Cervico-vaginal smear, Dysplasia, Colposcopy, Conization, Hysterectomy, Dakar, Senegal

22. Cervical neoplasia

00097

USE AND RESULTS OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN WOMEN HPV+ AND/OR ABNORMAL PAP SMEAR ATTENDED IN A REGIONAL SPANISH HOSPITAL. PRELIMINARY ANALYSIS

22. Cervical neoplasia

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Background / Objectives

A Coriolus versicolor-based (CV) vaginal gel is recently available In Spain to prevent and treat the HPV-dependent low grade cervical lesions. Recommended dose: 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months (except menstrual days).

To analyze how CV vaginal gel is being used in our hospital and to evaluate the treatment results in our patients.

Results

A retrospective, observational study. Medical records of patients who completed 3 or 6 months treatment period during 2017 were analyzed. Baseline characteristics of CV vaginal gel users were described.

Pre and post treatment number of patients with ASCUS/LSIL, positive-HPV and high-risk positive HPV were assessed.

Conclusion

A total of 86 medical records were analyzed. Most of them (84%) were treated for 6 months. Mean age was 38.4 years (from 18 to 72 years), 43.5% were vaccinated before treatment with CV vaginal gel, 32,5% were smokers and 42% used condoms regularly in all their sexual relationships. Baseline pap smear: Normal 11(13%), ASCUS 3 (3.5%), LSIL 65 (75.5%) and HSIL 7 (8%). HPV test was performed in 68 patients of which 57 (89%) were high risk HPV.

After treatment, reductions of 54% (from 68 to 31; p≤0.0001 Chi-Square test), 57% (from 68 to 29; p≤0.0001) and 58% (from 57 to 24; p≤0.0001) were observed in number of patients with ASCUS/LSIL, positive-HPV and high risk positive HPV, respectively vs baseline.

References

In our hospital, presence of LSIL is the main reason to prescribe the CV vaginal gel. In this preliminary analysis, significant reductions of patients with pap smear alterations and high-risk HPV were observed after 3-6 months application of CV vaginal gel.

00098

EFFICACY OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HIGH RISK HPV+ WOMEN. PRELIMINARY RESULTS.

22. Cervical neoplasia

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Background / Objectives

A Coriolus versicolor-based vaginal gel (Papilocare®) is recently available In Spain to prevent and treat the HPV-dependent low grade cervical lesions.

To evaluate the efficacy of the Coriolus versicolor-based vaginal gel to clear HPV and to normalize pap smear in high risk HPV+ women.

Results

An exploratory, prospective, observational non-controlled study. High risk HPV+ vaccinated and unvaccinated women older than 24 years were included during routine follow-up visits and treated with the recommended dose of Papilocare®: 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months (except menstrual days).

Primary endpoint: composite efficacy variable consists of percentage of patients with normal pap smear and/or HPV clearance at month 6 vs baseline. Secondary variable: percentage of patients clearing HPV 16-18 vs baseline.

Conclusion

A total of 86 patients, mean age 42.1 years (24 to 81) were included. At 6 months, 53% of women negativized pap smear and/or cleared HPV and were classified as responders to treatment. A total of 25 patients were positive to HPV 16-18 at baseline (12 and 13 with positive and negative pap smear, respectively). Overall, at 6 months, 48% of these patients cleared HPV 16-18 (50% and 46% of patients with positive and negative pap smear, respectively).

References

In these preliminary analyses, Papilocare® shows positive trend to improve pap smear alterations and HPV clearance in women infected by high risk HPV, after 6 months; these findings need to be confirmed upon analyses completion.

00099

CORIOLUS VERSICOLOR VAGINAL GEL IN THE TREATMENT OF HIGH-RISK POSITIVE HPV PATIENTS.

22. Cervical neoplasia

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Background / Objectives

In our center, about 25% of patients with high-risk HPV (HR+HPV) clear the virus at 12 months with a wait and see approach. Evaluate the efficacy of a Coriolus versicolor vaginal gel in HR+HPV patients.

Results

This was a retrospective, descriptive, observational study following the protocols of the ICO (Institut Català d´Oncologia – Hospitalet de Llobregat - Barcelona). Data of HR+HPV patients between 20 and 65 years with ASCUS, L-SIL (Group A) or normal cytology (Group B) treated with a Coriolus versicolor-based vaginal gel for 3 weeks and then alternating days until 6 months were included in a database. Both vaccinated and pregnant patients were excluded. Recruitment period: December 2016 to October 2017. Primary endpoint: composite efficacy variable consists of percentage of patients with normal cytology and/or HPV clearance at month 6 vs baseline. HR+HPV evaluation was performed by hybrid capture.

Conclusion

A total of 91 HR+HPV patients were included (Group A: 46 (50.5%) and Group B: 45 (49.5%)). 72.5% of patients negativized cytology and/or cleared HPV. In group A, 63% of patients normalize their situation (59% and 66.6% of patients with initial ASCUS and LSIL, respectively), no effect was seen in 24% and 13% worsened. In group B, 82.2% cleared or reduced viral load, 13.3% increased it and 4% (2 patients) were lost of follow-up.

References

Coriolus versicolor-based vaginal gel appears to be effective against ASCUS and L-SIL lesions caused by high-risk HPV. In HR+HPV patients with normal cytology, there is a clearance of the virus at 6 months of treatment. Further prospective studies are needed to confirm these exciting results.

00119

EVALUATING ErbB RECEPTOR PROFILE IN YOUNG PATIENTS WITH CERVICAL CANCER

22. Cervical neoplasia

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Background / Objectives

The aim of our study was to assess the expression and clinical significance of ErbB receptors in severe cervical dysplasia and cervical cancer specimens. The human EGF system plays an important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development. It is present in several tissues and has four receptors (ErbB-1, -2, -3 and -4) and numerous ligands. ErbB receptors are trans-membrane glycoproteins with an extracellular region containing two ligand-binding domains, a transmembrane domain and an intracellular domain with tyrosine kinase activity.

Results

We evaluated retrospectively tissue specimens from 75 young women with cervical precancer or cancer, managed in our institution. Among them, 33 patients had *in situ* and 42 patients had invasive cervical cancer. These specimens were immunostained for ErbB-2, -3 and -4. Tumors were scored based on the proportion of tumor cells stained. Immunostaining of 5% of tumor cells was considered as an optimized cut-off for tumor positivity.

Conclusion

Regarding ErbB-2 expression, 8 cases were positive (10.7%) and 67 cases were negative (89.3%). For ErbB-3 expression, 24 cases were positive (32%) and 51 cases were negative (68%). For ErbB-4, 37 cases were positive (49.3%) and 38 cases were negative (50.7%). A statistically significant correlation between ErbB-2 expression and invasive cervical cancer emerged in our study. All ErbB-2 positive

specimens originated from patients with invasive cervical cancer. Moreover all specimens from patients with *in situ* cervical precancer were ErbB-2 negative.

References

Dysregulation of the EGF system signaling network is implicated in various disorders. Loss of control of the cell functions mediated by this system is a hallmark of oncogenesis, being found in several types of human cancers where it becomes hyperactivated with various mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation).

Overepression and structural alterations of ErbB-1 are associated with higher grade, disease progression, poor survival and resistance to radiotherapy and chemotherapy. Overexpression of ErbB-2 is an indicator of a more aggressive clinical behavior. As for ErbB-3, despite it's overexpression is related with ErbB-2 positivity and lymph node involvement, a definitive relationship with poor survival has not been established. Finally, overexpression of ErbB-4 is related with favorable prognosis in breast and bladder cancer.

It is likely that ErbB receptor overexpression indicates of a more aggressive clinical behavior in cervical cancer patients. Future studies will further elucidate the clinical significance of ErbB receptors in this neoplasm.

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00125

RHABDOMYOSARCOMA OF THE CERVIX – CASE REPORT

22. Cervical neoplasia

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Background / Objectives

Rhabdomyosarcoma is defined as a malignant neoplasm which derives from embryonic muscle cells. In children, it is the most commonly discovered soft tissue tumor, whereas in adult, rhabdomyosarcomas are rare, representing less than 5% of soft tissue tumors and less than 1% of all malignant cancers. Histopathologically, rhabdomyosarcoma was classified by the Intergroup Rhabdomyosarcoma Study Groups into 3 major subtypes: embryonal, alveolar and undifferentiated. The surgical treatment for cervical rhabdomyosarcoma could be conservative or radical surgery with survival rates of vaginal and cervical lesions being reported to be of 96% and 60%, respectively.

Results

We present the case of a 46-year-old woman which addressed the clinic in mid 2017 due to an abnormal vaginal discharge. Gynecologic examination revealed a large 5/6 cm cervical mass with grape- like feature protruding into the vagina. A biopsy was performed and pathologic examination was consistent with embryonal type rhabdomyosarcoma. The patient refused further investigations and opted for local resection. She has since came back 2 times with recurrence of the mass, each time refusing radical surgery.

References

The case is particularly interesting due to the uncommon site of the rhabdomyosarcoma and the patients age.

00155

POSITIVE MARGINS AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE FOR CERVICAL INTRAEPITHELIAL NEOPLASIA: EXPECTANT MANAGEMENT AND FOLLOW-UP

22. Cervical neoplasia

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Background / Objectives

Early detection and treatment of Cervical Intraepithelial Neoplasia(CIN) has proven to be effective in reducing the incidence and mortality of cervical cancer. Loop Electrosurgical Excision Procedure(LEEP) is a less invasive treatment, associated with minor complications. Positive margins after LEEP(5-40%) is the most important predictive factor for CIN persistence/recurrence. However, management of these cases remain controversial, since often no CIN is observed during follow-up. Evidence supports individualized management: some patients profit from close follow-up while others benefit from a second LEEP or even hysterectomy as a definitive treatment. We studied 181 patients that underwent LEEP for CIN in our center, in order to identify persistent/recurrent cases and to determine if close follow-up and expectant management were advantageous, refraining more invasive procedures.

Results

We performed a retrospective study with descriptive and bivariable analysis, using SPSS Statistics. Data was based on clinical reports of patients treated between 2013-2017.

Conclusion

The average age of patients was 35,89±9,46 years-old. The majority came from primary care screening(56,35%;n=102). 45,86%(n=83) were multiparous, 54,1%(n=98) were using oral contraception and 33,7%(n=61) were smokers. Colposcopy was satisfactory and biopsy was performed in 97,8%(n=177) of patients. As for histologic definitive diagnosis, after LEEP, CIN1 was encountered in 13,8%(n=25), CIN2 in 33,1%(n=6), CIN 3 in 52,5%(n=95) and 0,6%(n=1) showed

chronic cervicitis. 26,5%(n=48) had positive margins. We did an expectant management in every patient(surveillance mean time of 31,22±15,14 months). From the positive margins group, 31,3%(n=15) had persistent/recurrent disease during follow-up, whereas only 6,48%(n=7) with free margins recurred, with statistical significant difference between groups(p<0,001; OR=8,27). In patients with positive margins, a positive Human Papillomavirus(HPV) during follow-up had significant association with persistent/recurrent disease(p<0,001; OR=23,7). Patients with persistent/recurrent CIN underwent a second LEEP(54,5%;n=12) or total hysterectomy(45,5%;n=10), depending on their characteristics, among them age (respectively 33,92±7,14 vs 43,50±9,38; p=0,01).

References

Positive margins after LEEP are associated with persistence/recurrence of CIN. In our sample the majority of patients didn't recur, which confirms that, in accordance with American and European guidelines, expectant management is acceptable, as long as follow-up is guaranteed. For patients with persistent disease any treatment option is acceptable, based on patient's risk factors and desire for future fertility.

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00343

GENITAL PROLAPSE ASSOCIATED WITH CERVICAL CANCER – A CASE REPORT

22. Cervical neoplasia

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Background / Objectives

Genital prolapse and carcinoma of the cervix are common entities but their association is rare. The displacement of the uterine cervix from the natural environment of the vagina may decrease the neoplastic process of viral infection which can explain the lower risk of cervical cancer in uterine prolapse. The best treatment approach in this clinical setting is not clearly defined and vary considerably among authors.

Results

We present a case of an ulcerated prolapsed uterus that presented in our department.

Conclusion

A 74-year-old woman, G3 P3, with a 9 years history of an uterine prolapse without prior cervical cancer screening. The reasons for medical visit were the onset of vaginal bleeding and genital prolapse increasing size. Physical examination revealed a complete and irreducible fourth-degree urogenital prolapse with induration of the entire vaginal mucosa, inflammatory signs and ulcerated lesions that made impossible to clearly identify the cervix (figure 1). No evidence of bladder or rectum involvement were present. Biopsies were performed and histopathology revealed squamous-cell carcinoma. A pelvic MRI revealed bilateral parametrial invasion and hydronephrosis. Computed tomography of the thorax and abdomen revealed no distant metastasis. She was staged according to the 2009 International Federation of Gynecology and Obstetrics staging system as at least FIGO IIIA. After a multidisciplinary board meeting, given the locally advanced stage and the volume of externalized prolapse, the patient was referred to end-life care measures, regarding her comfort, and died 1 month after the initial presentation.

References

This case highlights an uncommon association between cervical cancer and uterine prolapse with few published reports in the literature. The optimal treatment needs to be individualized in order to improve prognosis and quality of life.

00416

Cervical cancer in Catalonia. A systematic survey of new cases in a general hospital.

22. Cervical neoplasia

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Background / Objectives

It is known that most cervical cancers in Catalonia are diagnosed in women not attending screening programs. Monitoring of cervical cancer patients from Pathology departments can identify errors in prevention, diagnosis, follow-up and patient management.

Results

Since 2010 we have systematically collected clinical and pathological data from patients with a new diagnosis of cervical cancer, including age, screening history, symptoms, stage, cytology, histology and high-risk Human papillomavirus status (HPV).

Conclusion

From 1/2010 to 6/2018 one hundred and six cervical carcinomas were diagnosed in our department, which included 81 (76,4%) squamous cell carcinomas (SCC), 22 (20,8%) adenocarcinomas (ADC), 2 (1,9 %) adenosquamous carcinomas (ADSC) and 1 (0,9 %) clear cell carcinoma (CCC). In 41 cases (51,9%) there was no cervical cytology in the previous 3 years. In 63 patients there was cytology, of which 27 (54%) were screening-based: 5 (7,9%) negative and 58 (92,1%) positive. HPV test (HC2 or cobas) was performed in 45 cytology samples with a positive result in 93.3%. Regarding biopsies, HPV was present in 87 (82.1%) cases. The negative samples corresponded to 6/22 (27.2%) ADC, 6/81 (7.4%) SCC, 1 (50%) ADSC and 1 (100%) CCC. Clinical stage (FIGO 2009) was: 5 (4.7%) IA, 38 (35.8%) IB, 2 (1.9%) IIA, 37 (34.9%) IIB, 1 (0.9%) IIIA, 10 (9.4%) IVA, 2 (1.9%) IVB and in 9 (8.5%) cases it was

not found. In 82,9% IA/IB stages there was a recent cytology, while only 45.1% of higher stages (≥II) had it. HPV+ cases were younger (mean age =54,7y) than HPV - (mean age=62,1y).

References

Systematic collection of clinical and pathological data from cases with a diagnosis of cervical cancer in Pathology departments is manageable and procures monitoring. The detection of errors can improve the prevention and diagnosis of cervical cancer. Differences between HPV positive and negative cases were related to age and histological type. Patients with cytology detected cases presented with less advanced stage compared to symptomatic cases. HPV negative cervical cancer cases deserve further analysis in the forthcoming era of HPV based screening programs.

00497

THE ROLE OF HPV E6/E7 ONCOPROTEINS IN EARLY DIAGNOSTIC OF CERVICAL PRECANCEROUS LESIONS.

22. Cervical neoplasia

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Background / Objectives

The role of High Risk (HR) HPV mRNA E6/E7 expression as a predictive marker of high grade cervical precancerous lesions is shown in some studies (Fontecha 2016).). There are no studies in Latvia on E6/E7 mRNA expression in patients with cervical intraepithelial neoplasia.

Results

108 women aged 18-65 with abnormal cytology referred for colposcopy during their first visit to Reference Colposcopy Centre in Riga East Clinical University Hospital in July 2016 - July 2017 were included in the study. For each patient material from cervix for HR HPV E6/E7 common RNA was taken and under colposcopy control punch biopsy with a following histological examination was performed. HPV mRNA E6/E7 were identified by real time PCR test.

Conclusion

29 patients with low grade squamous intraepithelial lesions (LSIL), 70 with high grade squamous intraepithelial lesions (HSIL), 8 patients with atypical squamous cells of undetermined significance (ASCUS) and 1 patient with atypical glandular cells of undetermined significance (AGUS) were included in the study.

HPV E6/E7 RNA presence was found in 89/108 cases: significantly highest proportion of E6/E7RNA expression - 90.0% (63/70) was found in patients from HSIL cytology group; 72.4% (21/29) in LSIL group and 62.5% (5/8) in ASCUS group ($p<0.05$). CIN2+ histology report was strongly associated with positive HPV E6/E7

RNA – 89.6% (69/77) cases compared with 64.3% in CIN1. In patients with HSIL cytology, punch biopsy CIN 2+ results were detected in 89.6% (67/70 cases), 64.3% (18/28) in LSIL group ($p<0.05$). Punch biopsy histology results CIN 2+ in ASCUS group were detected in 3/8 cases and in patients with LSIL cytology in 9/29 cases. HPV E6/E7 RNA was positive in all of these 12 cases.

References

Our findings suggest that detection of HR HPV E6/E7 RNA simultaneously with cytology test may be a possible positive prognostic factor in early high grade cervical precancerous lesions diagnostic. More detailed studies for method standardizing are required.

00520

Cervical HPV and Solid Organ Transplant – a Risky Conundrum

22. Cervical neoplasia

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Background / Objectives

Malignancy risk is increased in transplant recipients. Risk of HPV related lesions is particularly relevant given the high prevalence of HPV infection in the general population. We aimed to assess the prevalence of HPV related lesions and possible predictive factors in transplant patients.

Results

Retrospective analysis of clinical data of transplant recipients observed in our institution between 2013 and 2017. Patients not under immunosuppressive therapy were excluded, as well as those who underwent bone marrow transplant or hysterectomy. Statistical analysis performed using Microsoft Office Excel® and IBM SPSS-Statistics®22.0.

Conclusion

A total of 171 women were included. Over two thirds (70,2%) were renal transplant recipients, while 22,8%, 5,3%, 0,6% and 0,6% had undergone liver, heart, lung and intestinal transplants, respectively. One patient had a double transplant (kidney and liver). Around 9% were carriers of a second graft. The majority of patients were parous (48,5%) and over half (52,63%) were postmenopausal.

An abnormal cervical smear result was present in 34 women (19,9%); 41,2% (n=14) had a negative HPV test and 50,0% (n=17) a positive one. In 17,6% of women (n=3) HPV16 was detected, while in 64,7% (n=11) other high risk (HR) types were present; both HPV16 and other HR types were present in 2 cases, and in 1 woman both HPV18 and other HR types were identified. HPV positive smears were as follows: 29,4% ASC-US, 52,9% LSIL, 11,8% HSIL and 5,9% concomitant HSIL and AGC. Staining with p16/Ki67 was positive in 29,4% (n=5).

Among women with abnormal smears, 6 (3,5%) underwent excision of the transformation zone (ETZ); 2 were ultimately classified as LSIL and 4 as HSIL. There were no cases of invasive carcinoma. After ETZ, one third maintained LSIL, one third resolved (NILM, negative for HR-HPV) and one third had not yet performed a control smear. Among women subject to expectant management, 6 (3 ASC-US and 3 LSIL) experienced regression of lesions, 3 remained stable (1 ASC-US and 2 LSIL) and 2 did not perform a follow-up smear.

Several factors seemed to influence the incidence of HPV related lesions, namely: age, age of first sexual intercourse, smoking, nulliparity, premenopausal status, history of condylomatosis and of a second graft (p value 0,001, 0,007, 0,016, 0,011, 0,028, 0,001, 0,007, respectively).

References

HPV related lesions were present in a fifth of transplant patients, with 3,5% having undergone EZT. HR-HPV types other than 16 or 18 were the most frequently encountered. Various factors seemed to influence the incidence of altered smears. These results highlight the need for closer gynecological surveillance in the transplant population.

00616

CERVICAL CANCER SCREENING PROGRAM IN LITHUANIA

22. Cervical neoplasia

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Background / Objectives

Background:

Cervical cancer in Lithuania is the fourth commonest cancer among women with malignancies. Since 1992 Lithuania have the increasing rates

in incidence of cervical cancer among the Nothern Europe countries and the highest in Baltic sea region countries. 2004 according Vilnius

Institute of Oncology data the cervical cancer incidence was 25.2/ 100 000, the mortality-12.8/ 100 000. In the middles of 2004 Lithuanian

Ministry of Health started cervical cancer screening programme.

Results

Guidelines for Screening and Policy Recommendations:

The programme includes screening of women in the age of 25-60 years. There are approximately 764 000 women of this age.
Screening interval - 3 years.
Cost of screening test for the women – free.
Primary test screening - conventional Papanicolaou test with Bethesda 2014 for reporting.
Pap test is investigated in 14 Pathology departments according quality control requirements.
438 primary health care centers are reimbursed for invitation of women and Pap smear taking.
The programme is coordinated by Coordinating Committee .

Conclusion

During 2004 - 2017 year were screened approximately 57 % of invited target age group women. Funds absorbtion rate was - 70 percent of the program budget.

Number of invitations from 2010 - 2017 period growing from 143 551 to 211 733. Number of screened women was 126 790 in 2017 year in comparison to 2010 (101646).

Cytological abnormalities in 2017 according " Sveidra" patient data base was: 1004 HSIL cases (0,79). LSIL cases - 1254 (0,99), ASC-US ratio was - 3,41% , inadequate ratio was - 3,03 %(3837). 9 squamous cell carcinoma cases was diagnosed in 2017.

According histological records CIS cases from the begining of programme 2004-2015 was changed dramatically from 60 to 634. Invasive cervical carcinoma cases statistics was from 468 to 364.

We did not observed significant decrease in cervical cancer death (208 death in 2007 and 200 death in 2012) and incidence (451 cases in 2007 and 487 cases in 2012).

References

Analysis of the data and the first expierence shows oportunistic sreening feature, inefective decentralized invitation system, the high

quality management of women with cytological abnormalities and indicates the need to improved the programme quality assurance,

creation of data base.

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23. Vaginal neoplasia

00194
MELANOMA MALIGNO DE VAGINA

23. Vaginal neoplasia

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Background / Objectives

O melanoma primário da vagina é um tumor extremamente raro, com menos de 250 casos publicados ao redor do mundo[1]. Corresponde a 3% de todos os tumores vaginais e 0,3% a 1% de todos os melanomas malignos, sendo mais agressivo se comparado a neoplasia cutânea, com altas taxas de recorrência e metástases[2]. Seu diagnóstico ocorre normalmente em fases avançadas. Assim, em virtude do mal prognóstico, exige abordagem terapêutica interdisciplinar planejada[1]. O presente trabalho possui como objetivo relatar caso de paciente com melanoma primário da vagina atendida no Hospital Universitário Professor Alberto Antunes (HUPAA), Maceió-AL.

Results

Estudo descritivo e observacional de relato de caso de paciente, M.U.S., 74 anos, sexo feminino, G21P18A3, natural e procedente de Campo Alegre-AL, portadora de melanoma primário de vagina encaminhada do interior do estado para serviço de oncologia do HUPAA. Para confecção do trabalho, os dados foram colhidos no prontuário da mesma.

Conclusion

Paciente com quadro de leucorreia e sangramento vaginal, associado a dor pélvica a cerca de 3 meses. Procurou assistência médica, onde foi evidenciada tumoração em região vaginal. Procedeu-se com biópsia local evidenciando pela imunohistoquímica melanoma maligno invasivo. Realizou então ressonância magnética (RNM) e PET/CT que demonstraram formação nodular heterogênea (medindo cerca de 5cm em seu maior diâmetro) situada na topografia vaginal/colo uterino em íntimo contato com parede anterior do reto, bem como com uretra. Programou-se então

exenteração pélvica. Contudo, ao realizar novo PET/CT 6 meses após o primeiro, evidenciou-se metástase pulmonar. Foi então programada terapia adjuvante com Decarbazina (DTIC). Apesar do tratamento paliativo, nova RNM mostrou aumento da massa tumoral (medido agora cerca de 13cm em seu maior diâmetro) com invasão de bexiga. Paciente realizou 4 ciclos de quimioterapia, vindo a falecer em seguida.

References

A sobrevida dos pacientes com metástase a distância é de aproximadamente 14 meses na maioria dos casos. Sendo assim, o estágio de apresentação o principal fator prognóstico nesse tipo de neoplasia[2]. Com isso, apesar das modalidades terapêuticas disponíveis (cirurgia, radioterapia, quimioterapia e imunoterapia) em virtude do diagnóstico geralmente tardio, seu prognóstico é sombrio[3]. Demonstrando, desse modo, a importância do acompanhamento primário com diagnóstico precoce, fato não observado em nossa paciente, que chegou ao nosso serviço com doença já avançada. Contudo, há anos DTIC tem sido a terapia padrão para o melanoma maligno cutâneo[3].

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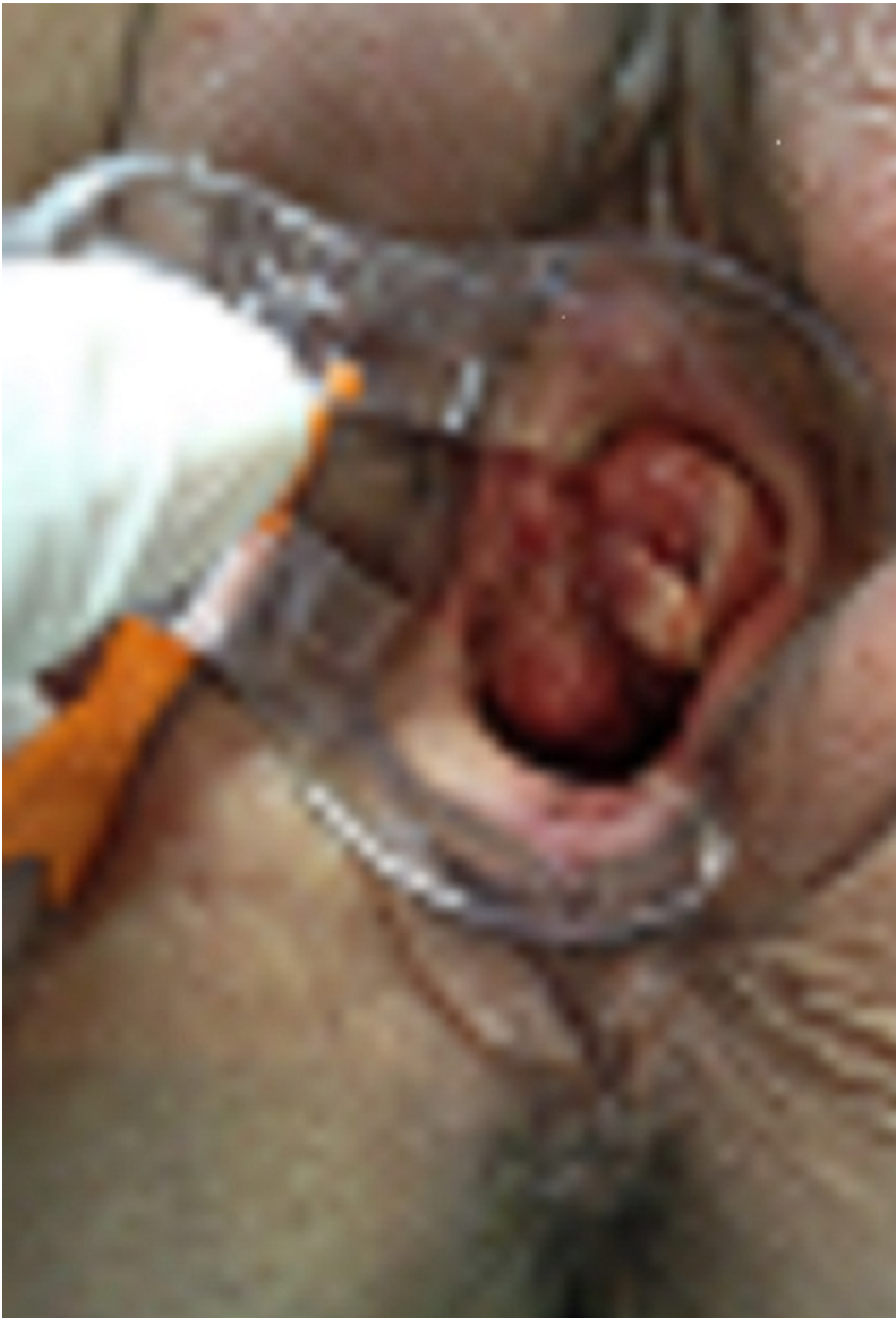

00341

HIGH-GRADE VAGINAL INTRAEPITHELIAL NEOPLASIA – A RETROSPECTIVE STUDY

23. Vaginal neoplasia

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Background / Objectives

Vaginal intraepithelial neoplasia (VaIN) is a rare disease, not completely characterized, corresponding to 0,4% of the intraepithelial neoplasias of the lower genital tract. Evidence supports that risk factors for the development of VaIN are similar to those found in cervical intraepithelial neoplasia. The prevalence of HPV infection ranges from 93% for VAIN 2/3 to 99% for VAIN 1. HPV 16 is the most frequently identified, followed by HPV 18. It is generally asymptomatic and the diagnosis is histologic. Excision and CO2 laser ablation are the mainstays of treatment. The aim of this study is to describe and analyse the diagnosis and treatment of high grade vaginal intraepithelial neoplasia (VaIN 2 or VaIN 3) in a secondary care hospital.

Results

Data from patients with diagnosis of VaIN 2 and VaIN 3 managed in our hospital between january 2012 and may 2018 were retrospectively collected. Demographic characteristics, general and gynaecologic medical history, methods of diagnosis, lesion characteristics, treatment procedures and outcomes were analysed.

Conclusion

Five patients presenting with high grade VaIN (3 VaIN 2 and 2 VaIN 3) were managed at our department. Mean age at diagnosis was 63,4 years ranging from 51 to 71 years. Only one had potential immunosuppression. All the patients had previous hysterectomy with associated cervical disease (CIN 3 or cervical cancer). The mean time between hysterectomy and diagnosis of VaIN was 34 months (ranging from 9 months to 8 years). VaIN was detected by an abnormal Pap smear in all cases (3

HSIL, 1 LSIL and 1 squamous cell carcinoma). White epithelium and punctuation were the most frequently colposcopic findings. All patients presented focal lesions in the upper third of the vagina and one had extension to the medium third of the vaginal mucosa. Four patients were treated by laser ablation and one treated with colpectomy. All patients had follow-up with cytological examination and vaginoscopy for therapeutic response evaluation. Remission was reported after the first ablation in one patient. Two patients had persistent disease and were treated with another laser ablation and one squamous cell carcinoma was detected 70 months after laser ablation. The patient treated with colpectomy had remission of the disease. There were no reported therapeutic side effects.

References

Despite the reduced sample size, the present study supports the maintenance of a long term cytologic screening after hysterectomy and a long term follow-up due to the recurrent character of VaIN.

00425

VAIN – A 7 YEARS HOSPITAL EXPERIENCE

23. Vaginal neoplasia

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Background / Objectives

The diagnosis of vaginal intraepithelial neoplasia (VaIN) has increased steadily over the past several decades.The true incidence of VaIN is unknown, but is estimated at 0.2-0.3 cases/100.000 women.

Nowadays we use a two-tiered nomenclature: LSIL for low-grade disease (VaIN1) and HSIL for high-grade disease (VaIN 2/3).

The prevalence of HPV in VaIN 2/3 is high (96%), with HPV 16 being the most frequently detected type (59%).

VaIN is consistently associated with prior or concurrent neoplasia elsewhere in the lower genital tract (50-90% have intraepithelial neoplasia or carcinoma of the cervix or vulva).

The purpose of this study is to review the cases of VaIN in our hospital and to compare the two groups: VaIN 1 and VaIN 2/3 in terms of demographics, patient history, hrHPV testing, therapy and follow-up.

Results

A retrospective study of women diagnosed with VaIN by colposcopy directed biopsy was performed at the Obstetrics and Gynecology Entre o Douro and Vouga Hospital Center between January 1, 2011, and August 1, 2018.

All available data including demographics, history of hysterectomy, cervical or vulvar pathology, histological information, cytology, and hrHPV testing results were recorded.

We divided our sample in two groups: group A (patients with VaIN 1) and group B (patients with VaIN 2/3).

Conclusion

During the seven years, we had 17 cases of VaIN (estimated prevalence of 2.7cases/100.000). The most common was VaIN 1 (58,8%), followed by VaIN 2 (23,5%) and VaIN 3 (17,7%).

In the group B the mean age was higher and a history of cervical or vulvar pathology was more frequent (71,5%).

The median interval between hysterectomy and VaIN diagnosis was 3,5 years , and the posthysterectomy status was more frequent in group B (57,1%).

Cytological findings: LSIL was more frequent in group A (50%) and in group B we didn't find any specific cytological pattern.The prevalence of HPV was similar in both groups (60% vs 57,2%), being the most frequently detected type hr-HPV (no 16 or 18) in group A; group B had the same percentage of hr-HPV (no 16 or 18) and HPV 16+ (28.6%).

In group A 100% of the patients didn't need treatment (just surveillance) and in group B 71,8% of patients underwent surgical treatment.

The recurrence/progression was higher in group B in the first year (57,1% vs 0%) and in the second year (14,2% vs 0%) of follow-up.

References

Despite the study limitations (its retrospective nature, missing data and a small sample size), this study showed that we have an estimated prevalence of 2.7cases/100.000 (higher than the literature), being the VaIN 1 the most frequent.

VaIN 2/3 has worse outcomes and it is associated with higher posthysterectomy status and cervical pathology.

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24. Vulvar diseases and neoplasia

00024

Vulvar Intraepithelial Neoplasia: Retrospective Study of 10 Years

24. Vulvar diseases and neoplasia

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Background / Objectives

Intraepithelial neoplasia of the vulva (VIN) occurs in about 2.86 per 100,000 women, with a growing incidence in the younger age groups. The usual VIN is typically found in women with HPV infection, young and smoker, whereas differentiated VIN (<5% of VIN) occurs in postmenopausal women, often associated with lichen sclerosus.

Goals:

To analyze the characteristics of patients diagnosed with VIN by vulvar biopsy.

To verify the therapeutic approaches and the relapses after treatment.

Results

This is a retrospective evaluation of 42 patients diagnosed with VIN in the cervical pathology unit of the Centro Materno Infantil do Norte from July of 2008 to June of 2018. The variables analyzed were: age at diagnosis; HPV co-infection; immunosuppression status; smoking; presence of a multifocal lesion, presence of a multicentric lesion; initial treatment modality; surgical margins; follow-up time; and recurrence of VIN. Statistical analysis with SPSS® software.

Conclusion

In the 42 cases of VIN only 2 cases was differentiated VIN (4.8%). The mean age at diagnosis was 55 years (29-83 years), with immunocompromised patients (33.3%) and smokers (27%) being significantly younger at the time of diagnosis ($p < 0.05$). 58% of immunocompromised patients had multifocal vulval lesions. 19 patients had

multicentric lesions (9 VaIN 2/3, 8 CIN 2/3, 3 AIN) the majority immunocompromised patients (p = 0.02).

The HPV-HR test was performed in 69% of the patients, being negative in only 17.2% of the tested.

The treatments included: extended excision of the lesion (50%), laser excision (30%), simple vulvectomy (17.5%) and laser ablation (2.5%). One case refused treatment and one case is still waiting for surgery. Surgical margins had high grade lesions in 36.8% of the cases and in 7,5% of histologies there was invasive lesion.

The mean follow-up time was 28 months, with 5 patients opting for private surveillance. A recurrence of the disease occurred in 30% of the cases, with an average of 29 months. In the comparison of surgical approaches, simple vulvectomy was found to confer greater disease-free time (p <0.05). There were no statistically significant differences in smoking, immunosuppression or affectation of margins for risk of recurrence. During follow up occured five cases of invasive vulvar carcinoma (12.5%).

References

We emphasize the importance of excisional treatments for the possibility of occult carcinoma and the long-term surveillance for the probability of recurrence. We found that the more conservative methods of exeresis presented shorter times until relapse. Follow-up is particularly important in immunocompromised patients because of the greater probability of multifocal and multicentric lesions.

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00165

CO2 LASER TREATMENT IN VIN LESIONS: WHAT IS ITS ROLE?

24. Vulvar diseases and neoplasia

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Background / Objectives

The incidence of vulvar intraepithelial neoplasia (VIN) has been increasing worldwide. This increase is more significant in young women (about 75% of cases), due to this fact it is necessary to institute conservative therapies in order to preserve the vulvar anatomy. The CO2 laser treatment has high clinical efficacy, allows microscopic precision with preservation of normal tissues, rapid healing with "ad integrum" restitution and a reduced number of complications.

To evaluate the role of CO2 laser in the treatment of VIN lesions.

Results

We present 2 cases of CO2 laser treatment in VIN lesions.

Conclusion

A 59 year old patient with persistent pruritic vulvar lesion with 6 months of evolution; had an incisional biopsy of the lesion that revealed "Bowen's Disease" (VIN III). History of total hysterectomy at age 39 due to a cervix HSIL. The examination had an extensive maculo-papular lesion, with hyperpigmented areas and hyperkeratosis from the middle 1/3 of the small left vulvar lip posteriorly to the lower 1/3 of the small right lip, involving the furcula and the entire perineum to the anus, but without vaginal involvement.
Extensive local excision of the CO2 laser lesion was performed under colposcopic control, and at the end the fulguration of the lesion margins was achieved. The histological study revealed high-grade VIN, with classic and multifocal aspects of VIN II and VIN III, with bowenoid and basaloid areas, with focal margin reach.

A 38 years old patient with vulvar lesion with 3 months of evolution had an incisional biopsy that revealed VIN II. History of cervical adenocarcinoma in situ 6 years ago in a excisional biopsy and Sjögren Syndrom with multiple vulvar ulcer. The examination revealed a leucoplasic lesion in both small lips with a condiloma in the furcula.

Cervical citology revealed ASC-H and incisional cervix biopsy HSIL with HPV 53 e 42 positive. Extensive local excision of the CO2 laser vulvar lesion and excisional cervix biopsy was performed under colposcopic control. The cervix biopsy revelead CIN II and vulvar biopsy showed HSIL.

Both patient presented an excellent aesthetic and functional result in the subsequent consultations, with no signs of local recurrence to date. Then they was vaccinated with the nonvalent vaccine.

References

CO2 laser surgery allows the treatment of VIN lesions on an outpatient basis, under local anesthesia with excellent cosmetic and functional results. The treatment can also be adjusted to the specific needs of each patient, with the possibility of calibrating the depth of the vaporized and removed tissues. Excisional treatment is the prefered method because it allows the histological evaluation of excised tissue and the detection of possible occult early invasion.

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25. Anal neoplasia

00251

DNA-HPV PCR: A TOOL TO INDICATE ANAL CYTOLOGY IN IMUNOSSUPRESSED WOMEN.

25. Anal neoplasia

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Background / Objectives

Anal cytology is a problem to implementation of cancer anal screening due to a lack of well-trained professionals, especially in immunosuppressed people.The objective of this study was to evaluate whether PCR for DNA-HPV screening could help identify cases with greater possibility of anal cytology with atypia to refer to specialized centers the positive cases.

Results

This cross-sectional study examined 31 kidney-transplanted women receiving immunosuppressive therapy at the General Hospital of Fortaleza in Brazil. Anal samples were collected and preserved in order to perform liquid-based cytology and a real-time PCR assay (Cobas 4800 [Roche Molecular Systems, Alameda, CA]) detecting high-risk HPV. The relative risk for atypical cytology was calculated for a confidence interval of 95%. The project was approved by the ethics committee of General Hospital of Fortaleza, Fortaleza, Brazil.

Conclusion

The patients ages ranged from 31 to 70 years old (mean: 42.6+10.4). Anal cytology was atypical in 35.4% of cases (ASC-US in 1[3.2%] and LSIL in 7[21.7%]). The presence of HPV was confirmed in 48.8% of the cases. a positive anal HPV test did correlate with a higher risk of atypical anal cytology (p=0.0197), yielding a relative risk of 10.18 (95% CI: 1.45–71.54).

References

The presence of HPV in an anal sample correlates with an increased risk of atypical anal cytology. HPV tests could be useful tools for identifying patients who require anal cytology.

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00291

Anal intraepithelial lesions in women with high-grade cervical intraepithelial neoplasia

25. Anal neoplasia

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Background / Objectives

Anal intraepithelial neoplasia is believed to be a precursor of anal cancer and it appears to be related to high-risk human papillomavirus. Women with genital neoplasia have been shown to be at increased risk for anal cancer.

The aim of this study is to describe the prevalence of abnormal anal cytology in women with high-grade cervical intraepithelial neoplasia and identify risk factors for abnormal anal cytology in this population.

Results

A cross-sectional study of 323 women from 2012 to 2017 with histopathological diagnosis of high-grade cervical intraepithelial neoplasia underwent anal cytology and completed a questionnaire detailing medical history and sexual behavior. All abnormal anal cytologies were submitted to anoscopy followed by a biopsy if pertinent. The hypothetical risk factors analyzed were: immunosuppression, tobacco use, lifetime number of sexual partners and history of anal intercourse.

Conclusion

Of total of 323 patients, 29 had a abnormal anal cytology (8,98%) which was: 3 with viral cytopathic effect (10,34%); 20 with ASCUS (68,97%); 3 with LSIL (10,34%); 1 with ASC-H (3,45%) and 2 with HSIL (6,90%). Of the 29 patients sent to anoscopy, 9 have missed the appointment (31%). The remaining was submitted to anoscopy: 7 had no alteration related to HPV and had no biopsy (35%); 4 had negative biopsies (25%); 9 had positive biopsies(45%): 1 revealed papilomatosis (5%); 1 a rectal adenoma (5%), 6 revealed condylomas (30%) and 1 revealed LSIL (5%).

From the risk factors analyzed, tobacco use was significantly associated with an abnormal anal cytology ($p<0.01$).

References

Tobacco use was significantly associated with an abnormal anal cytology and should be considered a risk factor. However, larger studies are needed to identify risk factors associated with abnormal cytology and anal intraepithelial neoplasia. We also need clarity to delineate the best screening method, screening frequency and appropriate treatment for anal intraepithelial neoplasia.

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00322

Does sampling strategy influence cytological and genetic findings in anal cancer screening of patients at risk?

25. Anal neoplasia

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Background / Objectives

Anal cancer (AC) screening of high-risk population can decrease the morbidity and mortality of this disease. High-resolution anoscopy (HRA) is a recommended method for AC screening when available. In case of the absence of HRA or a proctologist experienced in HRA, different strategies are considered. Especially those tests used in cervical cancer screening are of note for AC screening because of an analogy of the natural history of both diseases. Therefore, anal cytology and hrHPV mRNA detection might be effective tests for the detection of severe anal lesions. However, sampling strategy could affect the value of test´s results, in terms of adequate cell collection. We have focused on how cytological and HPV finding could differ in specimens sampled by a skilled nurse which is a routine practice, and by a proctologist during an ordinary anoscopic examination.

Results

120 anal smears from 60 Czech men having sex with men (MSM)/HIV positive MSM were collected into a liquid-based cytological vial using a damp dacron swab. One sampling was carried out by a proctologist during an ordinary anoscopic examination (AS) and another by a nurse during a routine check (RS). All samples were processed for cytology and tested for mRNA expression of 14 hrHPV types, with separate identification of HPV types 16,18, and 45, and finally genotyped.

Conclusion

In our study group, cytological finding ranging from NILM to HSIL were described. 19 % of samples had not sufficient cellularity for a credible cytological diagnosis. Cytology results of RS and AS differed in half of the patients. 50 % of cytological samples were not influenced by sampling strategy and routine and anal samples revealed the same diagnosis.

HPV mRNA test results differed between RS and AS to a lesser extent, namely in 38 % of patients. Moreover, when considering partial genotyping, HPV results of RS and AS differed in 51.6 % of patients. RS and AS usually shared identical HPV genotypes with a few exceptions.

References

According to our data both sampling strategies, i.e. routine and anoscopic, represent “blind” collection of cells without targeting the lesional tissue of the anal canal. An anal smear taken during an ordinary anoscopic examination does not seem to bring any improvement of cytological based AC screening under given circumstances, however, another sampling device is going to be tested for an increase of cellularity of samples. Using cytology and HPV tests for anal cancer screening, high-grade lesions could be detected in a high-risk population. Nevertheless, repeat sampling would probably increase the sensitivity of such a method.

References

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00403

ANAL CANCER SCREENING COMPLIANCE AND KNOWLEDGE AMONG HIV POSITIVE MSM IN THE CZECH REPUBLIC

25. Anal neoplasia

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Background / Objectives

HIV-positive men who have sex with men (MSM) are at increased risk of anal cancer. Prior to our study no regular screening program for anal cancer in the Czech Republic was available.

Results

Anal cancer screening was proposed to the HIV positive MSM attending Dermatovenereology and Infectious Disease Department Na Bulovce Hospital, Prague, the Czech Republic from July 2017 to June 2018. The blind rectal swab for anal cytology, DNA methylation and HPV testing was done immediately, anoscopy examination for each patient was scheduled.

Conclusion

During the one year period, anal cancer screening was proposed to 183 patients of whom 127 (69.4 %) agreed to participate. The age range was 18 to 63 years of age (mean 33 years). Prior to our study anal cancer screening has been proposed or performed in 14 (11.2 %) of the patients who entered the study. Only 17 (13.4 %) patients were aware of the increased risk of anal cancer. The blind rectal swab was performed in all of the patients, but the scheduled anoscopy examination underwent only 47 (37.0 %) patients. Only 2 (1.6 %) of the patients have been vaccinated against HPV.

References

The knowledge regarding anal cancer and its screening among HIV positive MSM in the Czech Republic seems to be very low. Compliance with blind rectal swabs was significantly higher than with anoscopy examination. The low compliance with anoscopy examination shows the need for sensitive diagnostic tests / biomarkers for triage of high-risk patients.

00588

Anal Cancer Risk Among People With HIV Infection in the United States

25. Anal neoplasia

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Background / Objectives

People with HIV infection have an elevated risk of anal cancer. However, recent calendar trends are incompletely described, and which population subgroups might benefit from cancer screening is unknown. With this study, we aim to quantified the risk of anal cancer among people with HIV infection in the United States during 1996 to 2012, by examining the associations of anal cancer incidence with demographic characteristics and prior AIDS diagnosis, and we assessed temporal trends. We also provide estimates of the cumulative incidence of anal cancer among subgroups of individuals with HIV with and without AIDS.

Results

We used linked data from HIV and cancer registries in nine US areas (1996 to 2012). We calculated standardized incidence ratios to compare anal cancer incidence in people with HIV infection with the general population, used Poisson regression to evaluate anal cancer incidence among subgroups of people with HIV and to assess temporal trends, and estimated the cumulative incidence of anal cancer to measure absolute risk.

Conclusion

Among 447,953 people with HIV infection, anal cancer incidence was much higher than in the general population (standardized incidence ratio, 19.1; 95% CI, 18.1 to 20.0). Anal cancer incidence was highest among men who have sex with men (MSM), increased with age, and was higher in people with AIDS than in those without

AIDS (ie, HIV only; adjusted incidence rate ratio, 3.82; 95% CI, 3.27 to 4.46). Incidence among people with HIV increased steeply during 1996 to 2000 (annual percentage change, 32.8%; 95% CI, -1.0% to 78.2%), reached a plateau during 2001 to 2008, and declined during 2008 to 2012 (annual percentage change, -7.2%; 95% CI, -14.4% to 0.6%). Cumulative incidence after a 5-year period was high for MSM with HIV only age 45 to 59 or ≥ 60 years (0.32% to 0.33%) and MSM with AIDS age 30 to 44, 45 to 59, or ≥ 60 years (0.29% to 0.65%).

References

Anal cancer incidence is markedly elevated among people with HIV infection, especially in MSM, older individuals, and people with AIDS. Recent declines may reflect delayed benefits of HIV treatment. Groups with high cumulative incidence of anal cancer may benefit from screening.

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26. Oral HPV infection

00233

PREVALENCE OF ORAL HPV INFECTION IN A PROSPECTIVE COHORT OF HIV-INFECTED AND UNINFECTED MEN WHO HAVE SEX WITH MEN: THE OHMAR PROJECT

26. Oral HPV infection

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Background / Objectives

Human Papillomavirus (HPV) plays a role in the development of head and neck squamous cell carcinoma (HNSCC). Oral HPV infection is more frequent in individuals with risky sexual behavior, such as men who have sex with men (MSM), than in the general population. We investigated the presence of HPV-DNA and high-risk (HR) HPV E6/E7 mRNA in oral rinse-and-gargles of HIV-infected and uninfected MSM enrolled in a longitudinal study (Oral HPV in Men At Risk, OHMAR Project).

Results

Participants were recruited among attendees of an STI/HIV Unit. They were thoroughly examined for the presence of lesions clinically suspicious for HNSCC and all clinically healthy subjects were enrolled. Oral samples were collected by using a commercial mouthwash for a 30 second rinse-and-gargle. Specimens were tested for the presence of HPV-DNA and HR-HPV E6/E7 mRNA by using the Linear Array HPV Genotyping Test and APTIMA HPV assay, respectively.

Conclusion

Overall, 310 MSM were enrolled, of which 117 HIV-infected (37.7%). These were mostly under cART (94.0%), and had undetectable HIV-1 RNA load (93.6%). HPV-DNA (any HPV type) was detected in 28/117 (23.9%) and 33/193 (17.1%) HIV-infected and uninfected subjects, respectively (p=0.14). HR-HPVs were found in 12/117 (10.3%) and 21/193 (10.9%) HIV-infected and uninfected MSM, respectively (p=0.86). Of the 33 HR-HPV positive MSM, 3 (9.1%) harbored HPV16 only, 8

(24.2%) HPV16 together with other HR types, and 22 (66.7%) only HR-HPVs other than HPV16. All the 33 HR-HPV DNA positive and 9 HR-HPV DNA negative random samples were tested with APTIMA HPV assay. Overall, 2/42 samples (4.8%), which were among those HR-HPV DNA positive, gave an invalid APTIMA result. All the HR-HPV DNA negative specimens tested APTIMA negative. HR-HPV E6/E7 mRNA was detected in 4 of the remaining 31 HR-HPV DNA positive oral rinses with a valid APTIMA test (12.9%). HR-HPV E6/E7 mRNA positivity was more frequent among the HPV16-positive participants than among those harboring only other HR types (2/11, 18.2% vs. 2/20, 10.0%, p=0.52).

References

Oral HPV infection is 2- to 3-fold more common among MSM than in the general population. Oral HPV prevalence is higher in HIV-infected MSM, although not significantly compared to the HIV-uninfected counterparts. Oral rinse-and-gargles from cancer-free MSM have detectable levels of HR-HPV E6/E7 mRNA. Although only a minor fraction of those harboring HR-HPV DNA were also positive for HR-HPV mRNA, HR-HPV E6/E7 mRNA testing of samples simply and non-invasively collected may help identify, among individuals without clinically evident lesions, those with transforming HPV infections, thus at greater risk for HPV-associated HNSCC.

00446

HPV IN ORAL CAVITY OF PATIENTS WITH BREAST CANCER

26. Oral HPV infection

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Background / Objectives

The Human Papillomavirus (HPV) is proven to be the main risk factor for cervical cancer, as well as for benign oral lesions. Recently, its role in the pathogenesis of breast and oral cancers has been investigated. Breast cancer is the second most prevalent type of neoplasm among women in Brazil, however, studies for detecting and genotyping HPV in these tumors are still scarce. Thus, the overall objective was to investigate the frequency of HPV and genotype in the oral cavity in patients with breast carcinoma.

Results

The research was conducted in patients attending in the mastology service of the Group of Education and Oncology Studies (GEEON) - Faculty of Medicine of the Federal University of Ceará (UFC), Brazil. The pilot project was conducted in 17 patients with breast cancer (case group) and 16 patients without breast cancer (control group). The HPV DNA was extracted from samples of the scrapings of the jugal mucosa and oropharyngeal swab. HPV detection and genotyping were performed through the multiplex nested PCR technique, through a set of primers that amplify the HPV E6/E7 consensus region. HPV genotyping amplified the E6/E7 region of the genome, followed by region-specific amplification for each viral type. Ten types of HPV were investigated: 6/11, 16, 18, 31, 33, 45, 52, 56, and 58. To statistical significance was used the t Student test and Fisher exact test to confidence interval of 95%. The project was approved by the Ethic Committee of UFC, nº 2.396.348-2017.

Conclusion

The patients in the group of breast cancer had mean age of 47.8 (±12.83) and in the control group was 49 (±11,40; p=0.49). In the study group HPV 6/11 was identified in oropharynx and jugal mucosa in two out of seventeen tested participants (11,76%). In the control group was identified HPV 6/11 in oropharynx and jugal mucosa in three

of sixteen participants (18.76%), and two (12.5%) participant in jugal mucosa with HPV 52 and other with HPV 33 (6.25%). In total it was detected HPV in 56.25% of the control group and 41.17% in the case group (p=0.49).

References

Despite the small number of cases studied, it was possible to observe that HPV is very frequent in the oral cavity, both in patients with breast cancer and without breast cancer. It will be necessary to study more cases for a more adequate conclusion.

27. HPV and oropharynx / Head and neck cancer

00100

DIFFERENCES IN THE PROGNOSIS OF HPV16 POSITIVE PATIENTS WITH SQUAMOUS CELL CARCINOMA OF HEAD AND NECK ACCORDING TO VIRAL LOAD AND EXPRESSION OF P16

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Patients with squamous cell carcinomas (SCCs) of head and neck cancers (HN) infected with HPV have more favorable prognosis than for those without infection (Ragin et al. 2007; Dayyani et al. 2010; O'Rorke et al. 2012). However, in more than 40% of HPV infected HNSCC patients progression of cancer disease is observed. Their identification is particularly important nowadays, because of ongoing trials concerning de-escalation of anticancer treatment in patients with HPV positive HNSCCs (Mirghani et al. 2015). Therefore, the aim of the study was to evaluate the impact of HPV16 load (VL-the number of virus genome copies per cell) and P16 expression on prognosis of patients with HNSCC.

Results

HPV16 presence was assessed in the group of 109 patients with HNSCCs by quantitative polymerase chain reaction (qPCR). VL (assessed by qPCR) and P16 expression (evaluated by immunohistochemistry) were analysed only in the subgroup of HPV16-positive tumours. These features were correlated with 5-year overall survival (OS) and disease-free survival (DFS).

Conclusion

HPV16 infection was found in 36 tumours (33.0%). Virus-positive patients had better OS and DFS than those without infection (P = 0.041 and 0.005). Among HPV16-positive HNSCCs, 18 (50.0%) had higher VL (median value > 6764.3 copies/cell) and 25 (73.5%) P16 over expression. The significant differences in OS and DFS (P = 0.008 and 0.004) were noticed according to VL, wherein 100% DFS was found for patients with higher VL. According to P16 expression, significant difference was found only for OS (P = 0.020). In multivariate analysis, VL (P = 0.045; HR = 2.795; CI 0.121–1.060) and the level of smoking (P = 0.023, HR = 2.253; CI 1.124–4.514) were independent factors affecting DFS of HPV16-positive patients.

References

On the basis of viral load, it is possible to differentiate prognosis of patients with HPV16-positive HNSCCs. In this subgroup, viral load has stronger prognostic potential than P16 expression.

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00312

HUMAN PAPILLOMAVIRUS INFECTION IN SINO-NASAL INVERTED PAPILLOMA: AN ITALIAN EPIDEMIOLOGICAL STUDY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Inverted Papillomas (IP) are benign epithelial tumor of the ciliated epithelium located innasal cavity and paranasal sinuses. Natural history usually includes dysplasia, in situ, and invasive squamous cell carcinoma(SCC).Local and distant invasivenessand high recurrence rateare the three distinctive features. Several etiologies have been investigated, from chronic inflammations,to allergy, environmental pollution, tobacco and/or occupational exposure, infections. Detection of HPV has raised the issue of its etio-pathogenic role in IP occurrence, as well as in malignancy progression. Aim of the study was to assessthe HPV prevalence in IP lesions and its potential heterogeneity in Italy.

Results

A total of 77 patients withIPwere recruited: they underwent endoscopic surgical therapyin 2 university Italian hospitals.Samples were collected from 62 and 15 patients with IPonly and IP with SCC, respectively. Moreover, a control group of 31 patients with normal mucosa was enrolled. DNA extraction was carried out using DNAeasy Blood & Tissue Kits (QIAGEN) and HPV detection and genotyping were performed using the Anyplex II HPV-28 kit (Seegene).

The HPV prevalence in patients with IPwas 11.7%, with 6 samples positive for HPV-6, one for HPV-11, and 2 for HR-HPV (HPV-39 and -56, respectively). Only one (6.7%) SCC was HPV positive. HPV was not found in the control group. No significant differences in prevalence and genotype distribution were found by gender,agegroups, and geographic areas.

References

Our study suggests a marginal role ofHPV in IP. Further studies are needed to understand the prevalence of LR-HPV genotypes and their priming action on cell replication. RNA detectionusing E6 and E7 transcripts can help further elucidate the IP pathogenesis.

00319

PSYCHOLOGICAL IMPACT OF PATIENTS LIVING WITH HEAD AND NECK CANCER: A SYSTEMATIC LITERATURE REVIEW

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Head and Neck Cancer (HNC) includes malignant tumors that develop in the mouth, pharynx, larynx, salivary glands, noses and sinuses. Worldwide, HNC accounts for more than 550,000 cases and 380,000 deaths annually.1 A meta-analysis estimated the HPV-attributable proportion of HNC to be 45.8% for the oropharyngeal cavity, 24.2% for the oral cavity, and 22.1% for the larynx.2 The aim of this study was to investigate the psychological impact of HNC.

Results

A systematic literature review (SLR) of health related quality of life in patients with HNC was conducted in MEDLINE, EMBASE, Cochrane CENTRAL and PsycInfo. Studies in English and published in the last ten years were selected when pre-set eligibility criteria were met. Studies in patients with HNC that reported patient-related outcomes from questionnaires specific to psychological impact, such as the Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI), were included. When the HADS-Anxiety score was >7, HADS-Depression score was >7, HADS-Total score was >14 or BDI score was >10, patients were considered psychologically distressed.

Conclusion

Twenty-four studies reporting HADS or BDI scores in HNC patients were identified. Eight of the 24 studies reported psychological distress in patients with HNC from Japan, The Netherlands, Canada, United Kingdom, Brazil, Germany and The United States (US). The characteristics of these eight studies are presented in Table 1.

HADS and BDI scores were measured at different time points: at baseline, at the end of a treatment (radiotherapy, chemotherapy or surgery) and during follow-up visits (3 weeks to 5 years). Five studies reported a psychological distress for the HADS-Total score (>14) at baseline or in post-treatment follow up. All studies that reported BDI scores (n=3) showed that HNC patients presented a mild mood disturbance (score: 11-16; n=2) or a borderline clinical depression (score: 17-20; n=1). The association between HPV and HNC was not stated among the included studies.

References

As shown in eight of the 24 studies included in our SLR, HNC can cause psychological distress in patients according to both the HADS and BDI tools and irrespective of age, country, length of follow up or gender. Moreover, a three-fold higher incidence of suicide has been reported in HNC compared with the general US population.3 It is unclear whether psychological distress differs between patients with HNC caused by HPV and those with other etiologies. This warrants further evaluation.

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Table 1: Studies on HNC psychological impact included in the systematic review

Author & year	Country	Study time period	Patient characteristics	Age	Time point	N	HADS-D Mean (SD)	HADS-A Mean (SD)	HADS-T Mean (SD)	BDI Mean (SD)
Ichikura 2018	Japan	2013	HNC patients (90.5% male) - Group of patients smoking, drinking, seeking support, or engaging self-distraction	40-80+	Post-treatment follow-up	79	NR	NR	NR	**11 (7.4) [BDI-II]**
Kobayashi 2008	Japan	2005-2007	Patients who were scheduled for surgery for HNC - Low self-esteem based on Rosenberg self-esteem scale	62	Preoperatively	20	5.8 (2.2)	6 (1.7)	11.8	NR
					Post-treatment follow-up (6 months)	20	**11.8 (4.3)**	4.4 (3.9)	**18**	NR
			Patients who were scheduled for surgery for HNC - High self-esteem based on Rosenberg self-esteem scale		Preoperatively	38	3.6 (3.1)	4.4 (1.9)	8	NR
					Post-treatment follow-up (6 months)	38	3.2 (2.7)	2.5 (2.0)	5.7	NR
Krebber 2016	The Netherlands	2009-2012	HNC treated patients who scored positive for psychological distress (HADS Total >14, Anxiety >7 or Depression >7)	61.7	Post-treatment follow-up (time frame of 37 months)	135	**8.77 (3.61)**	**8.84 (3.84)**	**17.39 (6.27)**	NR
Moubayed 2015	Canada	2011-2012	HNC patients diagnosed at least 12 months prior to clinic visit that had completed initial treatment (pre-treatment predictors of depressing symptoms: >3 medications, current smoking, > 14 drinks per week or T3/T4 disease stage)	<60 for n=112 and >60 for n=97	Post-treatment follow up: 38.7 months	209	0.8 (0 predictors)	NR	NR	NR
					Post-treatment follow up: 38.7 months		3.5 (1 predictor)	NR	NR	NR
					Post-treatment follow up: 38.7 months		3.9 (2 predictors)	NR	NR	NR
					Post-treatment follow up: 38.7 months		5.6 (3 predictors)	NR	NR	NR
					Post-treatment follow up: 38.7 months		**8.3 (4 predictors)**	NR	NR	NR
Clarke 2014	United Kingdom	2007-2008	Patients aged ≥18 with HNC at least 6 months post-treatment	60.47	Baseline	49	5.88 (3.8)	6.69 (4.7)	12.57	NR
					Baseline (female)	18	6.61 (3.56)	**8.17 (5.23)**	**14.78**	NR
					Baseline (male)	31	5.45 (3.93)	5.84 (4.18)	11.29	NR
					Post-treatment follow-up (9 months)	20	4.8 (2.96)	6.8 (4.69)	11.6	NR
Sawada 2012	Brazil	2009-2010	HNC patients undergoing radiotherapy	30-90	Start of treatment	41	NR	NR	NR	9.44 [BDI]
					End of treatment	41	NR	NR	NR	**12.32 [BDI]**
Singer 2012	Germany	NR	HNC patients from the radiation–oncology department	58	First day in hospital	113	NR	NR	**14.22**	NR
					6 months after admission	56	NR	NR	**14.85**	NR
Chen 2009	USA	2006-2007	Patients with a primary diagnosis of non-metastatic HNC undergoing radiotherapy	55 (median)	Before treatment	40	**8.4 (5.5)**	7.5 (4.3)	**15.9**	**12.6 (10.0) [BDI-II]**
					End of treatment	40	**11.2 (5.5)**	6.9 (5.0)	**18.1**	**18 (12.2) [BDI-II]**

BDI: Beck's Depression Inventory; HADS-A: Hospital Anxiety and Depression Score anxiety scale; HADS-D: Hospital Anxiety and Depression Score depression scale; HADS-T: Hospital Anxiety and Depression Score total; HNC: head and neck cancer; NR: Not reported

Notes: HADS scoring (either for Depression or Anxiety): Total score: 0-7 = Normal, 8-10 = Borderline abnormal (borderline case), 11-21 = Abnormal (case); BDI scoring: 1-10: These ups and downs are considered normal, 11-16: Mild mood disturbance, 17-20: Borderline clinical depression, 21-30: Moderate depression, 31-40: Severe depression, over 40: Extreme depression. Scores showing psychological distress are in bold.

00378

ABSENCE OF DISRUPTIVE TP53 MUTATIONS IN HIGH-RISK HUMAN PAPILLOMAVIRUS-DRIVEN NECK SQUAMOUS CELL CARCINOMA FROM UNKNOWN PRIMARY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Patients with head and neck squamous cell carcinoma (SCC) may not rarely present with neck metastases without evidence for a primary tumor. Similarly to oropharyngeal SCC (OPSCC), a substantial proportion of neck SCC from unknown primary (NSCCUP) contains transcriptionally active high-risk human papillomaviruses (hrHPVs) infections and show better overall survival rates. p53 oncosuppressor mediates radiation-induced apoptosis and *TP53* mutations have been linked with increased resistance to ionizing radiation. hrHPV-driven OPSCCs are considered to contain sufficient intact p53 to preserve a radiosensitive phenotype. To enforce the evidence for causality between hrHPV infections and NSCCUP and provide biological basis for treatment de-intensification trials in this clinical entity, we searched for *TP53* mutations by analyzing exons 4 to 10 in NSCCUP.

Results

FFPE tissue were available from 70 NSCCUP patients from Germany, Italy, and Spain. HPV-driven cases were defined by presence of E6*I mRNA together with at least one additional marker (HPV-DNA and p16high). *TP53* mutations were searched by analyzing exons 4 to 10. PCR products were sequenced by fluorescent capillary electrophoresis.

Conclusion

Of the 70 NSCCUP samples, 26 (37%) harbored a transforming HPV infection. Exons 4 to 8 of the TP53 gene were screened for mutations in all patients, while exons 9 and 10 were additionally sequenced in 57 patients. Sequencing success ranged from 77% for exon 4 to 91% for exon 9. TP53 sequencing resulted in the identification of 19 single mutations. These included 16 disruptive alterations (84%), comprising missense (n=7) located within the DNA binding domain (amino acids 102-292), frameshift (n=4, resulting in nonsense mutations at a later amino acid position), and nonsense mutations (n=5, four within the DNA binding domain). When comparing NSCCUP patients with disruptive *TP53* mutation in any exon (n=16) with patients without disruptive mutation but with complete sequence of exon 4-9 (n=32), all disruptive mutations were found in patients with non-HPV-driven NSCCUP (16/31; 52%) and in none of the 17 patients with HPV-driven NSCCUP (P=0.0002).

References

In a relevant fraction of cases, NSCCUP is a HPV-driven entity showing transcriptionally active hrHPV infection and harboring a wild-type *TP53* sequence. HPV-driven NSCCUP may benefit from treatment de-intensification obtained not only by restricting the prophylactic irradiation of the upper aero-digestive tract to the OP and its corresponding lymphatic pathways but also, perspectively, by including these patients in clinical trials evaluating dose de-escalation strategies for HPV-driven OPSCC.

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00417

THREE CASES OF HPV-RELATED OROPHARYNGEAL CANCER WITH GOOD COURSE DESPITE NONCOMPLETION OF (CHEMO)RADIOTHERAPY

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

HPV status is an important factor in the treatment of oropharyngeal cancer. Recently, the establishment of minimally invasive treatment for HPV-related cancers is one of the urgent issues in the treatment of head and neck cancers. We report three cases of HPV- positive oropharyngeal cancer with good course despite noncompletion of radiotherapy.

Results

We reviewed 113 cases of oropharyngeal squamous cell carcinoma treated at Osaka University Hospital and Osaka Rosai Hospital between 2013 and 2015. (Chemo) radiotherapy was used to treat 87 cases, with noncompletion of the radiotherapy in three cases, which were all HPV-DNA positive and p16 positive. We analyzed the records of these three cases for the reasons for noncompletion of treatment, the effect of primary treatment, and the subsequent course. UICC 7th edition was used for staging.

Conclusion

Case 1, Tonsillar carcinoma, T4aN3M0, 61-year-old man, PS1

The planned treatment was 70Gy radiation and six courses of weekly chemotherapy, but due to severe pneumonia, the treatment was changed to 45Gy radiation and three courses of chemotherapy. At the end of the treatment, the cancer remained clearly in both the primary and the lymph node in the CT, but after 12 weeks, the lesion was not detected by PET-CT. The patient is currently alive without relapse for 39 months.

Case 2, Tonsillar carcinoma, T4bN2cM0, 71-year-old woman, PS2

Treatment was completed with 56Gy radiation therapy and five courses of chemotherapy due to multiple compression fractures of the thoracic spine and lumbar vertebra caused by falls. The tumor was not detectable by PET-CT after 12 weeks of treatment. The patient is currently alive without relapse for 53 months.

Case 3, Tonsillar carcinoma, T2N2bM0, 53-year-old man, PS1

The planned treatment was 70Gy radiation therapy, but treatment was terminted at 48Gy due to delirium and gastrointestinal bleeding. After radiotherapy, tonsillectomy and neck dissection were performed, but pathologically no cancer was detected. The patient is currently alive without relapse for 58 months.

References

We examined three cases of HPV-positive oropharyngeal cancer with good course, despite noncompletion of the planned treatment. The patients, who are currently alive with relapse, had been given irradiation doses of 45Gy, 48Gy or 56Gy. These cases may offer suggestions for minimally invasive treatment of HPV-related oropharyngeal cancer.

Case	Age	Sex	Primary site	TNM	Treatment	Outcome
1	61	Male	Tonsil	T4aN3M0	CCRT RT45Gy CDDP60mg/m^2	39 M NED
2	71	Female	Tonsil	T4bN2cM0	CCRT RT56Gy CDDP100mg/m^2	53 M NED
3	53	Male	Tonsil	T2N2bM0	IMRT RT48Gy	58 M NED

00467

Droplet digital PCR quantification suggests that higher viral load correlates with improved survival in HPV-positive oropharyngeal tumours.

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Previous studies in small cohorts have shown an association of HPV viral load with improved survival rates in oropharyngeal cancer (OPC). Although HPV-positive OPC patients have a better prognosis, there is still an HPV-positive group who have poor outcomes. Therefore, a single test that can better delineate patient outcomes would be desirable. Our objective was to analyse viral load by a highly accurate technique, droplet digital absolute PCR quantification (ddPCR), in a cohort of 134 cases of HPV-positive oropharyngeal tumours on whom clinical outcome data, including survival data, were available.

Results

The present analysis was performed on a subset of a population based patient cohort diagnosed with OPC in 2013, who were the subject of a previous audit on HPV status and survival outcomes. 121 samples were designated as positive for HPV16 using the Diamex Optiplex genotyping test. Viral load was determined for these samples, using ddPCR assays specific for HPV16 L1 and E6.

Viral load was classed as “high” if more than 5 copies of the L1 portion of HPV16 genome per cell were detected. Analysis of the association between high versus low viral load and overall survival in addition to hazard of death & disease progression was performed; adjustments for sex, age, deprivation, smoking, alcohol consumption and stage (TMN and ICON) were carried out.

Conclusion

Of the the 121 HPV16-positive samples, 100/121 samples were positive using the ddPCR assays. The range of viral load (VL) was from 0.0014 to 304 genome copies per cell with a mean of 30.9 (SD 51.1).

In the univariate analysis those with a high viral load have a lower hazard of death and recurrence (p=0.027). The majority of samples had an E6 to L1 ratio ~1. However, 10 samples had a ratio >1 (range=1.3 to 2.3) and 9 samples had a ratio <1 (range=0.3 to 0.7), suggesting variation in episomal versus integrated genome numbers. Full data in addition to adjusted analyses according to demographic and behavioural attributes will be presented.

References

These data suggest that HPV viral load may be informative in determining patient outcomes.

00477

High risk human papillomavirus genotypes detected in recurrent respiratory papillomatosis by Linear array and NSG.

27. HPV and oropharynx / Head and neck cancer

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Background / Objectives

Recurrent Respiratory Papillomatosis (RRP) is a benign illness, mostly associated with low risk papillomavirus types 6 and/or 11. This papillomatosis is a public health issue representing an economic burden both to the public health system and the patients. The objective of this work was to identify any other HPV types in larynx biopsies, besides the formerly reported types 6 and 11.

Results

We collected 30 larynx biopsy samples from adult patients in the Otorhinolaryngology Service at the Hospital de Especialidades del CMN SXXI, Mexico City. Virus genotyping was done on DNA from each sample, by two techniques: 1) Sanger's sequencing of PCR amplimers from MY09/MY11 and/or GP5+/GP6+ primers; and 2) Roche Linear Array HPV genotyping kit. Also, in 20 out of the 30 samples we used the next generation sequencing analysis in a DNA sequencing platform (NSG).

Conclusion

By Sanger’s sequencing we identified HPV-6 in 18 samples and HPV-11 in 12 samples. By Linear Array we got the same results, except that four of the samples were co-infected: one with HPV types 6 and 11; two with HPV 6 and 16, and one with HPV 11 and 16. In the 20 samples sequenced by NSG, we found that nine samples were infected with high risk HPV types: six samples with HPV-16, five samples with HPV-58 and four samples with HPV-31; all 20 of them were co-infected with other high and low risk HPV types.

References

We identified some high risk HPVs (HPV types: 16, 58 and 31) in addition to HPV6/11 prototypes in larynx biopsies.The prevalence of the HPV-6 and/or HPV11 in all the RRP samples analyzed, as well as the coinfection with HPV-16 in some cases, allows us to suggest that the administration of the quadrivalent prophylactic vaccine would be useful at least in the patients with aggressive and recurrent forms of laryngeal papillomatosis in their therapy.

28. HPV and associated skin diseases

00621

Development of G-quadruplex mediated HPV antiviral drugs

28. HPV and associated skin diseases

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Background / Objectives

Human papillomaviruses (HPVs) are causative agents of benign and malignant lesions of the genital tract [1]. Most HPV-related cancers are due to oncogenic HPVs namely types 16, 18, 31, 33 and 45 [1]. Until now, several G-rich sequences were found in the HPV genome that can form stable G-quadruplexes (G4). Some of them include high-risk HPV types, responsible for the majority of cases of cervical cancer [1]. Viral G4s are usually located in regulatory regions of the genome and are implicated in the control of key viral processes [1]. G4 ligands have mediated mechanisms of action at the genome and transcript level in latent infections promoting a way for cutting-edge therapeutic approaches in the treatment of HPV related cancer [2]. Threfore, we report the screening of ligands in terms of their ability to recognize G4 found in HPV genomes. The ligand C_8 was evaluated in terms of transcription, replication and viral proteins production.

Results

Human cervical keratinocyte lines stably maintaining HPV DNA (HCK16-5 and HCK18C) were grown in monolayer culture using E medium in the presence of mitomycin C-treated J2 3T3 feeder cells. J2 3T3 feeder cells were grown in DMEM medium supplemented with 10% FBS and gentamycin. HPV organotypic raft cultures were then established. The raft cultures were then fed by diffusion from below with E medium supplemented with 100, 250 and 500 nM C_8 or DMSO alone as a solvent control. The raft cultures were allowed to stratify and differentiate for 20 days.

Conclusion

HPV G4s were shown to possess a high degree of polymorphism upon ligand binding and stabilization which may have impact on transcription, replication and viral proteins production. We evaluated the antiviral effect of C_8 in raft epithelial cultures infected with episomal high-risk HPVs 16 and 18. Treatment with increasing concentrations of C_8 had a pronounced thinning of the raft of HPV18 comparing to the control. The

quantification of total viral genomes showed a decreasing number of HPV18 genome copies, from $4x10^5$ to $7.6x10^3$ genomes/µL at 250 nM of C_8. The exposure of cervical cells to C_8 concentration of 250 nM resulted in a 10-fold decrease in HPV18 viral titers. This data suggests that while C_8 has a lower effect on viral genome amplification, it may play a role in viral genome encapsidation.

References

In summary, our results propose original binding modes of several ligands towards high- and low- risk HPV G4s structures which have never been reported before, using a variety of different techniques. These G4 structures were found within regions involved in transcription, replication and viral proteins production. The antiviral effect of C_8 was confirmed on organotypic raft cultures containing replicating HPV18 and C_8 was able to decrease the viral load by several orders of magnitude.

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29. Genital warts

00407

ANOGENITAL WARTS IN PREGNANCY

29. Genital warts

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Background / Objectives

Anogenital warts are benign proliferative lesions caused by human papillomavirus (HPV) infection. Approximately 90% are associated with HPV types 6 and 11. During pregnancy, genital warts tend to rapidly enlarge and multiply. Eradication or reduction of lesions is the primary goal of treatment, mainly to prevent physical obstruction to vaginal delivery and reduce the transmission to the sexual partners and fetus.

Results

Descriptive study of 61 medical files of pregnant patients with macroscopic genital warts followed and treated at Obstetrics A Department of CHUC between 2001 and 2017.

Conclusion

The average age of our women was 28.9±5.6 years. 4.9% (n=3) of patients were referred in the first, 41.0% (n=25) in the second and 54.1% (n=33) in the third trimester of pregnancy. 32.1% of the pregnant patients were multiparous and 28.0% were smokers. The average number of previous sexual partners were 2.8±1.8. Reasons for referral were: genital warts in 80.3% (n=49), vulvar itching in 4.9% (n=3), abnormal cervical cytology in 4.9% (n=3) and cervical lesion in 9.8% (n=6).

A histological study was obtained from 52 patients, confirming condylomata acuminata.

In the 9 remaining patients, the evaluation was deferred until after delivery, due to advanced gestational age. As for the treatment (n=44), surgical excision was performed in 50.0% (n=22), trichloroacetic acid (TCA) in 47.7% (n=21),

electrocautery in 36.4% (n=16) and silver nitrate in 9.1% (n=4). 18 patients were submitted to more than one different procedure. 3 patients were submitted to cervical loop electrosurgical excision procedure due to extensive cervical condylomatosis, in the first trimester of pregnancy. Of the 61 patients, 4 were submitted to cesarean section due to extended genital warts (3 with cervical and 1 with vulvar warts) obstructing the birth canal, without any previous treatment (all referred at the end of pregnancy).

Over the studied years, our report showed no trend in the incidence of anogenital warts in pregnancy.

References

Surgical excision was the preferred treatment for genital warts. As vaginal delivery does not seem to increase the risk of laryngeal papillomatosis, cesarean section was reserved for cases of large genital warts that might obstruct the birth canal or result in heavy bleeding.

30. Sexually transmitted diseases and HIV infection

00132

RETROSPECTIVE COHORT STUDY OF MEN WHO HAVE SEX WITH MEN THAT ARE INFECTED BY THE HUMAN IMMUNODEFICIENCY VIRUS AND WERE SUBMITTED TO HUMAN PAPILLOMAVIRUS SCREENING IN THE ANAL CANAL.

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted infection in European and North American countries. It causes significant morbidity in women, men who have sex with men (MSM) and immunocompromised. Squamous cell carcinoma (SCC) of the anus is the most common non-AIDS-defining epithelial neoplasia in human immunodeficiency virus (HIV)-positive patients, which is associated with HPV infection. The aim of the study was to characterize anogenital HPV morbidity in HIV-infected patients through polymerase chain reaction (PCR) and/or anatomopathological examination of associated anal canal lesions.

Results

Retrospective 8-year study of HIV-infected male patients submitted to HPV DNA analysis on the anal canal by PCR. Population was characterized according to the following parameters: demographics, antiretroviral therapy (ART), HIV viral load and CD4+ T cells count at the moment of specimen collection, subtypes of identified HPV, biopsy result when performed and prescribed treatment. Data were obtained consulting the patients' clinical process and were treated statistically using Microsoft Excel 2016®.

Conclusion

Of the 71 patients undergoing screening, HPV was identified in 85.9% (n=61). The average age was 41.8 ± 15.8 years old. 88.5% (n=54) were under ART and 73.7% (n=45) had undetectable HIV viral load. The mean CD4+ T cells count was 559 cells/mm3. The most frequent subtype was HPV-16, identified in 29.5% (n=18), followed by HPV-6, HPV-11 and HPV-53 found in 27.9% (n=17), 24.6% (n=15) and 23% (n=14), respectively. In 24.6% (n=15) of the screened patients only one HPV subtype was identified and in 19.7% (n=12) more than 5 HPV subtypes were identified in the same patient. Biopsy was performed in 41% (n=25): in 24% (n=6) condylomas were identified, 20% (n=5) had no changes and in 20% (n=5) had evidence of SCC. There were 32.8% (n=20) of patients submitted to treatment, and of these 50% (n=10) did topical application of imiquimod cream, 30% (n=6) electrocautery and 20% (n=4) had surgical excision. Tumor-related mortality was of 3.3% (n=2).

References

Our results emphasize the importance of screening the presence of HPV infection in HIV-infected patients, especially in MSM. However, we highlight the small number of patients in whom the presence of HPV in anal canal was investigated, which reinforces the importance of creating an internal referral protocol and a systematic investigation of the virus in this population. In this way, it is intended to reduce the incidence of neoplasia and consequently associated morbidity and mortality.

00145

HIV INFECTED PREGNANT WOMEN DATA COMPLETENESS FROM STATE OF ESPIRITO SANTO - BRAZIL PUBLIC DATABASE

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

The completeness of HIV infected pregnant women data registered in Notifiable Diseases Information System (SINAN) is important to provide accurate information for a better definition of their epidemiological characteristics. Thus, it becomes possible to offer action planning subsidies in order to control mother to children HIV transmission. This study, therefore, aimed at assessing the completeness of HIV infected pregnant women data reported in Espírito Santo, southeastern Brazil between 2007 and 2012.

Results

It is a descriptive analytic study based on secondary data of HIV infected pregnant women registered in Notifiable Diseases Information System (SINAN), in Espirito Santo State, southeastern Brazil between 2007 and 2012. The scores used were: excellent (variable shows less than 5% of incomplete coverage), good (5% to 10%), fair (10% to 20%), poor (20% to 50%) and very poor (50% or higher). The linear trend equations were calculated for incompleteness over time, with a 5% statistical significance. Data were grouped according to the information type: information in the notification, pregnant woman, residence, prenatal, delivery and newborn.

Conclusion

495 HIV infected pregnant women were reported in the SINAN. There were serious gaps in the completeness of the SINAN database of HIV-infected pregnant women in the state of Espirito Santo. There was higher frequency completeness as fair, poor and very poor in prenatal care, delivery, and newborn information. There were two variables with a downward incompleteness trend: municipality where prenatal took place (value of R 2 = 0.697; p = 0.039) and the Unified Health System card number (value of R2 = 0.916; p = 0.003). On the other hand, the delivery health unit (R2 value = 0.761; p = 0.023) had an upward incompleteness trend.

References

The results of this study indicated an essential data high non-completeness regarding prevention information on mother-to-child transmission of HIV. We suggest continuing education and training for the notifier professional to make them able to record all data and accurate information in order to support the control of mother-to-child transmission of HIV.

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Table 1. Non – completeness frequency by field and classification according to Romero & Cunha regarding data on HIV infected pregnant women notified between 2007 and 2012 in the State of Espírito Santo - Brazil.

Fill fields (n = 495)	N	%	Classification
NOTIFICATION			
Notification date	0	0,0	Excellent
State of notification	0	0,0	Excellent
City of notification	0	0,0	Excellent
District	0	0,0	Excellent
Health Unit of notification	0	0,0	Excellent
Gestational trimester of notification	40	8,1	Good
PREGNANT WOMAN			
Name	0	0,0	Excellent
Birth date	16	3,2	Excellent
Pregnant Woman Mother's name	10	2,0	Excellent
Age	17	3,4	Excellent
Race	17	3,4	Excellent
Schooling	121	24,4	Poor
Employment	378	76,4	Very poor
Telephone number	186	37,6	Poor
National Health Card	391	79,0	Very poor
RESIDENCE			
State of residence	0	0	Excellent
City of residence	0	0,0	Excellent
District of residence	0	0,0	Excellent
Neighborhood	17	3,4	Excellent
Street	15	3,0	Excellent
Postal Address Code	378	76,4	Very Poor
PRENATAL			
Held prenatal	11	2,2	Excellent
Pregnant Woman on SISPRENATAL	375	75,8	Very Poor
State of prenatal assistance	107	21,6	Poor
City of prenatal assistance	46	9,3	Good
Health Unit of prenatal assistance	120	24,2	Poor
HIV laboratory evidence	11	2,2	Excellent
Date of HIV diagnosis	11	2,2	Excellent
ARV use during prenatal assistance	62	12,5	Fair
Initial date of ARV use during prenatal assistance	157	31,7	Poor
DELIVERY			
Delivery date	0	0,0	Excellent
Delivery city	118	23,8	Poor
Delivery health unit	249	50,3	Very Poor
Delivery type	131	26,5	Poor
AZT use during delivery	128	25,9	Poor
NEWBORN			
Reproductive Outcome	124	25,1	Poor
AZT prophylaxis in newborn (hours)	153	30,9	Poor

N: Absolut Frequency; %: Relative Frequency.

00315

Epidemiology of HPV anal infection in person with HIV attending a Sexually Transmitted Infection Clinic in Brazil

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

Background: HIV-positive patients have significantly more anal cancer than the general population. It is estimated that 75 to 80 percent of sexually active people will acquire a genital tract infection by HPV before age 50. Objective: To estimate the prevalence and persistence of anal infection, genotype distribution and correlates with anal HPV infection in HIV-infected patients attending a Sexually Transmitted Infections (STI) clinic in Vitoria, ES.

Results

Methods: Cross section was performed including demographic and behavioral assessment. Anal specimens were collected for cytology and for HPV testing by PCR followed by reverse line blot analysis for genotyping and sequence alignments for HPV16 variants determination.

Conclusion

Results: A total of 223 patients were enrolled for the study, 143 females and 80 males. Mean age was 40.6 years and the average education was 9.1 years. A total of 31.8% initiated sexual activity before 15 years old and 73.1% reported anal sexual activity. Previous STI was reported by 67.9% patients; 61.8% had undetectable viral load and 81.5% were taking antiretroviral therapy (ART). The prevalence of anal abnormal cytology was 29.3% and 20.8% had abnormal anoscopy. The prevalence of HPV infection of any type was 68.0 %, and high-risk HPV types were 50.2%, among then, HPV 16, 51 and 52 were the most frequent. A total of 38.8% individuals had multiple HPV types. The HPV16 European variant was the most frequent (71. 4%). There was persistence of 52.3% of anal HPV infection of the same type in patients who have the collection in three consecutive visits. Twenty-nine patients had positive biopsy for anal intraepithelial neoplasia (AIN) (18.3%).

References

Anal HPV infection was common among HIV-infected persons. Anal cytology screening for HIV-infected, particularly for those with anal HPV infection and history of STI, will increase the likelihood of detecting anal intraepithelial neoplasia.

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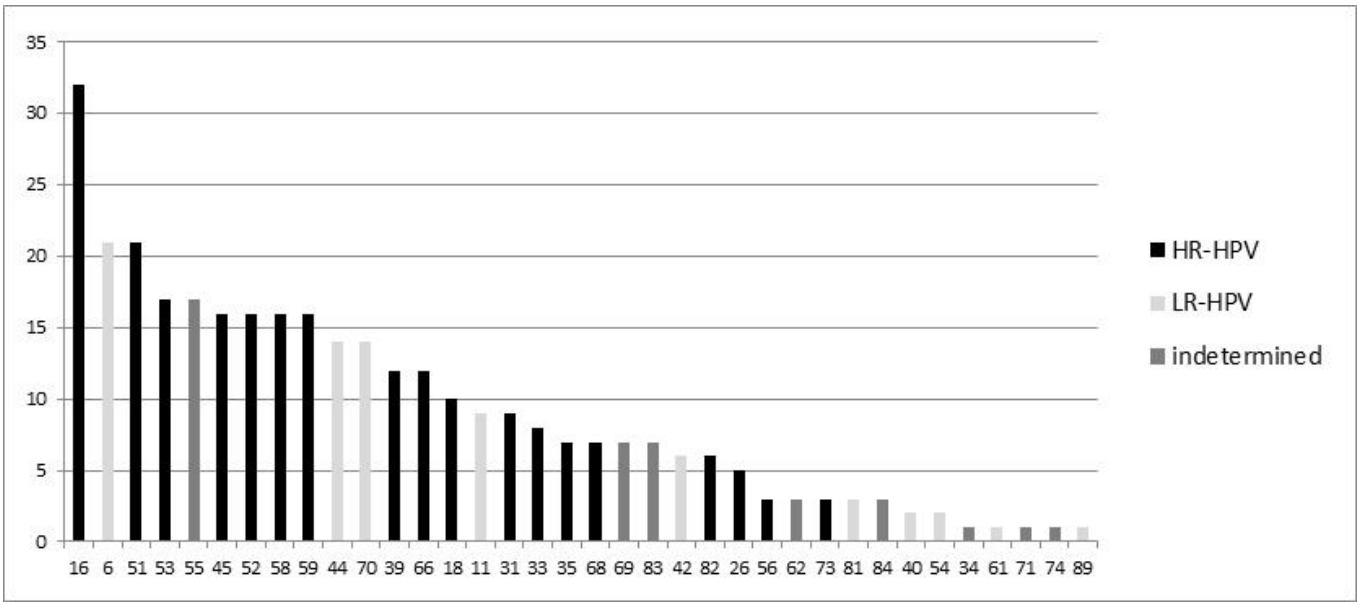
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LR-HPV
indetermined

00483

Papanicolaou (PAP) smear changes and cervical HPV prevalence in women living with Human Immunodeficiency Virus

30. Sexually transmitted diseases and HIV infection

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Background / Objectives

Women living with Human Immunodeficiency Virus (WLHIV) currently experience longer live expectancy due to antiretroviral therapy. They are at greater risk for human papillomavirus (HPV) infection and persistence, increasing the risk of abnormalities in the cervical cells and invasive cervical cancer. Although the incidence of HIV-defining cancers has declined, cervical cancer has remained high among WLHIV. Our goal is to characterize PAP smear results and HPV prevalence in HIV-positive women in follow-up on Gynecology appointment of Centro Hospitalar e Universitário de Coimbra between 2013 and 2017.

Results

Analysis of clinical records. All women who had at least one appointment and one PAP smear between 2013 and 2017 were included. HPV test was performed by COBAS System. The statistical analysis was made with SPSS.

Conclusion

There were 232 WLHIV observed between 2013 and 2017. Among these, 11,6% (n=27) had co-infection with hepatitis C virus (HCV), 1,3% (n=3) with hepatitis B virus (HBV) and 0,4% (n=1) had a triple infection (HIV, HCV and HBV). They were in average 46,6 [18-80] years-old on the first visit and 61,2% (n=142) were pre-menopausal. Prevalence of HPV infection was 15,5% (n=36). Other types of high-risk HPV including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (OHRHPV) were presented in 91,7% (n=33) of women; among these, 15,2% (n=5) were co-infected

with HPV16 and 9,1% (n=3) with HPV18. Only 8,3% (n=3) of women tested positive only for HPV16.

Cervical smear was NILM in 67,2% (n=156) of women; 3,2% (n=5) tested positive for HPV [1,9% (n=3) for OHRHPV and 1,3% (n=2) for HPV16]. ASC-US were presented in 15,1% (n=35) of women. In this group, 34,3% (n=12) were HPV positive: 25,7% (n=9) for OHRHPV, 5,7% (n=2) for HPV16 and OHRHPV and 2,9% (n=1) for HPV16 alone. PAP smear revealed LSIL in about 16,4% (n=38), 47,4% of which (n=18) were HPV positive. All of them had OHRHPV and 33,3% (n=6) were co-infected with HPV16 or 18. HSIL at pap smear was present in only 0,9% (n=2) of women and only one was positive for OHRHPV. In this period one woman had a diagnose of epidermoid carcinoma of the cervix.

Logistic regression analysis showed HPV infection to be associated with smoking and a higher number of sexual partners ($p<0,01$).

References

The prevalence of HPV in our population of WLHIV is lower than in other studies reported in literature. Almost all women with positive HPV had OHRHPV serotypes and the serotype less prevalent was HPV18. The prevalence of HPV is increased in higher grade lesions and HPV infection is associated with smoking and a higher number of sexual partners in this population.

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31. Conventional therapies

00158

PLACENTAL GROWTH RESTRICTION IN HIV-INFECTED WOMEN AS A SIGN OF EARLY PREGNANCY AGGRESSION

31. Conventional therapies

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ESPIRITO SANTO FEDERAL UNIVERSITY - UFES (Brazil)

Background / Objectives

There are few studies on placental growth disorders including HIV-infected pregnant women. Most of them use less than optimal growth assessment and are confined to one or two placental measures at a time, mainly to placental weight and placental-to-fetal-weight ratio. It is important to search for growth disorders in a comprehensive set of placental measures in HIV-infected women to improve the quality of care. This study aimed to determine the occurrence of placental growth disorders in low income, antiretroviral users, HIV-infected pregnant women attending a public hospital in Brazil.

Results

Out of 250 cases of HIV-infected pregnant women with terminations between 2001 and 2012 in a public tertiary University Hospital in Vitória City, Espírito Santo State, Brazil, we selected singleton pregnancy cases with ultrasound validated gestational age (GA) in which there was a comprehensive set of at birth measures: fetal weight (FW), placental weight (PW), placental-to fetal weight ratio (PFR), chorionic plate area (PA), and mean thickness (PT). These dimensions were converted to z score for GA and categorized as small (s), adequate (a) and large (l) for GA by the -1,28 < z < +1,28 usual criteria. The frequency of growth disorders was calculated for each individual measure and for all possible combination.

Conclusion

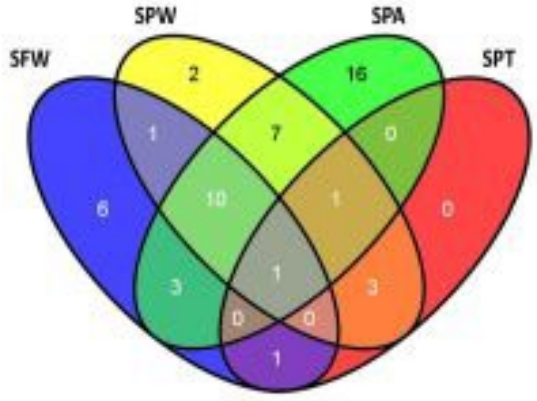
109 cases met the inclusion criteria. Some growth disorders were observed in 51 (58,6%) cases: FW, PW, PFR, PA, and PT were SGA in 20,2%, 22,9%, 10,1%, 34,9% and 5,5%, and LGA in 4,6%, 0%, 42,2%, 0% and 11,9%, respectively. SFW only occurred in 9,17% and small placental growth disorders only (any combination) in 26,6%. Out of 22 SFW, there were 54,5% SPW, 63,6% SPA, and 9,1% PT, but

among 87 non-SFW there was an additional 14,9% SPW, 27,6% SPA, and 4,6% SPT.

References

In this HIV-Infected Pregnant women casuistry, growth restriction occurred more often in the placenta than in the fetus and mostly in the form of a small placental area than from small placental thickness, pointing to an early (I and II trimester) aggression.

Small Gestational Age Placental Measurements in SGA Fetal Weight Distribution



SGA – Small for Gestational Age; SFW – Small Fetal Weight; SPW – Small Placental Weight; SPA – Small Placental Area; SPT – Small Placental Thickness

00424

OBSTETRIC OUTCOMES AFTER EXCISION OF THE CERVICAL TRANSFORMATION ZONE - A RETROSPECTIVE 8-YEAR STUDY

31. Conventional therapies

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Background / Objectives

Most of the pre-invasive cervical disease and early cervical cancer occur in women at the childbearing age, and the local conservative therapies, usually the excision of the cervical transformation zone (ETZ), result in sequels that are a concern for future pregnancy. As a consequence of this technic the cervix becomes shorter, which may lead to a higher risk of obstetric complications, such as preterm delivery.

Objectives: To evaluate the impact on the obstetric outcomes in women submitted to cervical ETZ due to pre-invasive cervical disease and early cervical cancer, in Madeira Islands.

Results

Descriptive retrospective longitudinal study of the obstetric outcomes in women with previous cervical ETZ, between 2009 and 2017, in Hospital Dr. Nélio Mendonça (HNM). Several variables where collected from the patient files: age, reason of the procedure, histological result and size of the cone, parity, number of abortions, pregnancy complications, weeks of pregnancy and method of delivery. All the ETZ were carried out with diathermic loop or by the classical method.

Conclusion

There were 29 women with a previous cervical ETZ that became pregnant, counting a total of 31 pregnancies. The mean age at ETZ was 32 years old and 33 years old during pregnancy. From the sample 37% were nulliparous. The main reason for the procedure was a cervical citology with a high-grade squamous intraepithelial lesion. Regarding obstetric outcomes, 45% had a delivery at term, 10% a pre-term delivery, 13% a spontaneous abortion, 13% a voluntary termination of pregnancy, 3% an ectopic pregnancy and 16% were still pregnant at the end of the study. The rate of preterm birth was 18%. The mean cone length in women with birth at term was 9 mm

and 13 mm in the pre-term group. Lastly, 76% had a vaginal delivery and 24% had a caesarean delivery.

References

As already described in other studies, women with this type of procedure have an increased risk of pre-term delivery, and therefore should be considered as a high-risk pregnancy, mostly if the ETZ cone is longer. Our results are consistent with the literature, since the overall rate of preterm deliveries on our hospital is 6%, and in women with ETZ we demonstrated a higher rate. Therefore is important to assess the cervical length at the beginning of the pregnancy to stratify the risk of pre-term delivery in these women.

00426

3-YEAR STUDY OF EXCISION OF THE CERVICAL TRANSFORMATION ZONE IN WOMEN IN MADEIRA ISLAND – ARE WE MEETING THE QUALITY INDICATORS?

31. Conventional therapies

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Background / Objectives

Excision of the transformation zone (ETZ) is indicated in a variety of reasons, that can range from an excisional procedure of a malignant lesion, to discordance between the cytology and the colposcopy results. This procedure has not only a diagnostic purpose, as in some cases it consist on the treatment. As an invasive procedure it is associated with some complications, the most frequent is haemorrhage from mild to severe, and also can lead to stenosis or cervical insufficiency.

Objectives: Characterize the woman submitted to cervical ETZ on Hospital Dr. Nélio Mendonça (HNM), in Funchal, from 2015 to 2018.

Results

Descriptive retrospective longitudinal study of woman submitted to cervical ETZ from July 2015 to July 2018, in the HNM. Several variables where collected from the patient files: age, risk factors for HPV (smoker status, sexual partners and age of first intercourse), the reason for the procedure, vaccination status, cytology, colposcopy findings, histological result, margins and size of the cone, and follow-up.

Conclusion

The total number of procedures was 151, and mean age was 38 years old. All the ETZ were carried out with diathermic loop or in some cases by the classical method. From the sample 13% were nulliparous, 25% were smokers or ex-smokers, the mean age of the first sexual intercourse was 18 years old, and in mean each women had a history of 3 sexual partners. The main reason for referral to the cervical pathology appointment was an abnormal result in the cervical cytology (15% LSIL, 37% HSIL and 21% ASC-H) and all of these women were submitted to a colposcopy previously to any treatment.

In most cases a biopsy was performed before ETZ (81%) and the main results were 46% cervical intraepithelial neoplasia (CIN) grade 2, 7% CIN grade 2/3 and 21% CIN grade 3. There was no registry of early complications from the ETZ. The main histological results from the cones were 35% CIN 2, 10% CIN 2/3 and 31% CIN 3. Also, were diagnosed 5 invasive cervical carcinoma (3%). 78% of the cone margins were free, and just 15% of the cones had no dysplasia. Lastly, 75% of these women initiated the vaccine against HPV.

References

Cervical ETZ is an effective, simple and safe method for the diagnosis and treatment of premalignant lesions and early stage cervical cancers. It’s important to have algorithms for the referral to this procedure, to minimize unnecessary ETZ and maximize the benefits for the women.

32. Economics and modelling

00154

COST-EFFECTIVENESS OF THE NEWLY IMPLEMENTED HPV-BASED SCREENING PROGRAMME IN THE NETHERLANDS

32. Economics and modelling

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Erasmus MC, University Medical Center Rotterdam, Department of Public Health, Rotterdam, The Netherlands - Rotterdam (Netherlands)

Background / Objectives

In 2017 the Dutch cervical cancer screening programme has switched from cytology to the HPV-test as the primary screening test, using five instead of seven lifetime screens. The aim of this study was to quantify both costs and the effects of this programme change.

Results

The microsimulation model MISCAN was used to calculate the number of screening tests, colposcopies, CIN/cancer diagnoses, cancer deaths, life years, QALYs gained and costs for the old and the new screening programme. Costs and effects were discounted annually by 4% and 1.5% respectively. Univariate sensitivity analyses were performed adjusting test characteristics of cytology, costs of screening tests, participation in HPV self-sampling and utility losses for false positive referrals.

Conclusion

The new programme reduces the cervical cancer mortality from 217 to 184 per 100.000 women simulated (-15%) and the incidence from 577 to 503 (-13%) compared to the old programme combined with a cost reduction of 20%, mainly caused by the reduction in number of screening rounds. Although the new programme results in 214% more referrals to colposcopy of women without CIN2+ (from 938 to 2,943 per 100.000 women simulated), it is still more cost effective (€3,497/QALY) than the old programme (€5,741/QALY). The new programme remained more cost-effective in all sensitivity analyses.

References

Although the new programme increases the amount of unnecessary referrals substantially, causing negative consequences for individual women, it decreases the cervical cancer incidence and mortality and reduces costs on the population level, making it a more cost-effective programme compared with the cytology based programme.

00166

THE EFFECT OF AN HPV GENDER-NEUTRAL VACCINATION PROGRAM ON VACCINE HESITANCY

32. Economics and modelling

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Background / Objectives

In Denmark, access to public financed HPV (Human Papilloma Virus) vaccination for 12-years old females has been an option since 2009. Boys are not included in the program. From 2009 to 2013 vaccination rates were high (>70%) but in 2014, 2015 and 2016 the vaccination rates were low (34%-57%) which may reinforce the argument for inclusion of boys in the program.

In addition, the nine-valent (HPV9) vaccine is now the applied vaccine in the program. Therefore, we present updated modelling analyses of vaccination which take the reduced vaccination rates and the improved protection from the HPV9 vaccine into account.

Results

A dynamic HPV transmission cost-effectiveness model was calibrated to a Danish setting and used to estimate the incremental costs and effects associated with different vaccination strategies compared to screening only. In the modelling, the actual vaccination rates for the first 9 years (vaccination of 12-years old females only) were applied. That is, gender-neutral strategies with vaccination of 12-years old boys via a public financed program (i.e. vaccination rates higher than 5%) were included from year 10 and onwards. Among others, the incremental effects were estimated as number of avoided HPV-related cancers, pre-cancers and deaths.

Conclusion

The updated model simulations show that this recent observed vaccine hesitancy in the long run (100 years) markedly affect the number of avoided HPV-related cancers.

If the 2016 female vaccination rate of 34% is maintained, the number of avoided HPV-related cancers will decline with 33% compared to a scenario where the future

vaccination rate is higher (60%).
In the scenario with maintained low vaccination rates (34%), inclusion of boys in the vaccination program will increase the number of avoided HPV-related cancers with almost 17%. In the scenario with future vaccination rates of 60%, gender-neutral vaccination will increase the number of avoided HPV-related cancers with 12%.

The gender-neutral vaccination program will improve the protection in females and males as the number of avoided HPV-related cancers and deaths increase, especially for anal, penile and head & neck cancer.

References

From a public health perspective, attention to the low vaccine coverage should be paid as it leads to an increasing number of HPV-related cancers and deaths. Initiatives that increase the vaccine confidence should be supported. In addition, gender-neutral HPV-vaccination should be considered as vaccination of boys increase the number of avoided HPV-related cancers, pre-cancers and deaths – especially when the female vaccination rates are low.

00485

COSTS AND HEALTHCARE RESOURCE UTILIZATION FOR CERVICAL CONIZATION IN MID-ADULT WOMEN IN THE UNITED STATES

32. Economics and modelling

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Background / Objectives

Cervical conization with Loop Electrical Excision Procedure (LEEP) or cold knife conization (CKC) is a standard treatment option for pre-cancerous cervical lesions caused by human papillomavirus (HPV). The estimated incidence for conization in mid-adult women is 1.7-1.8/1000, and the costs associated with these procedures are not well described and potentially preventable by HPV vaccination. We aimed to estimate healthcare resource utilization (HCRU) and costs of conization in the US.

Results

We performed a retrospective cohort study using the Truven MarketScan® database, a large healthcare claims database in the US. All mid-adult women (27-45 years old) who were treated from 2012-2016 by LEEP or CKC (CPT code 57522, 57520) or both LEEP and CKC within 30 days were included if they had continuous enrollment ≥6 months before and 1-month after the procedure. Exclusion criteria included pregnancy, cancer diagnosis, or immunocompromised status and invalid cost data (i.e. cost<=$1 or 99th %ile of top costs). All-cause (i.e., medical claims for inpatient/outpatient visits and/or admissions and prescriptions irrespective of disease or procedure) and conization–specific HCRU and costs were estimated for the 30-days post-conization. Conization-specific costs included costs of admissions, outpatient visits, follow-up tests (pap smear, HPV test, colposcopy), and post-operative complications (hemorrhage, vaginal bleeding/discharge, fever, post-

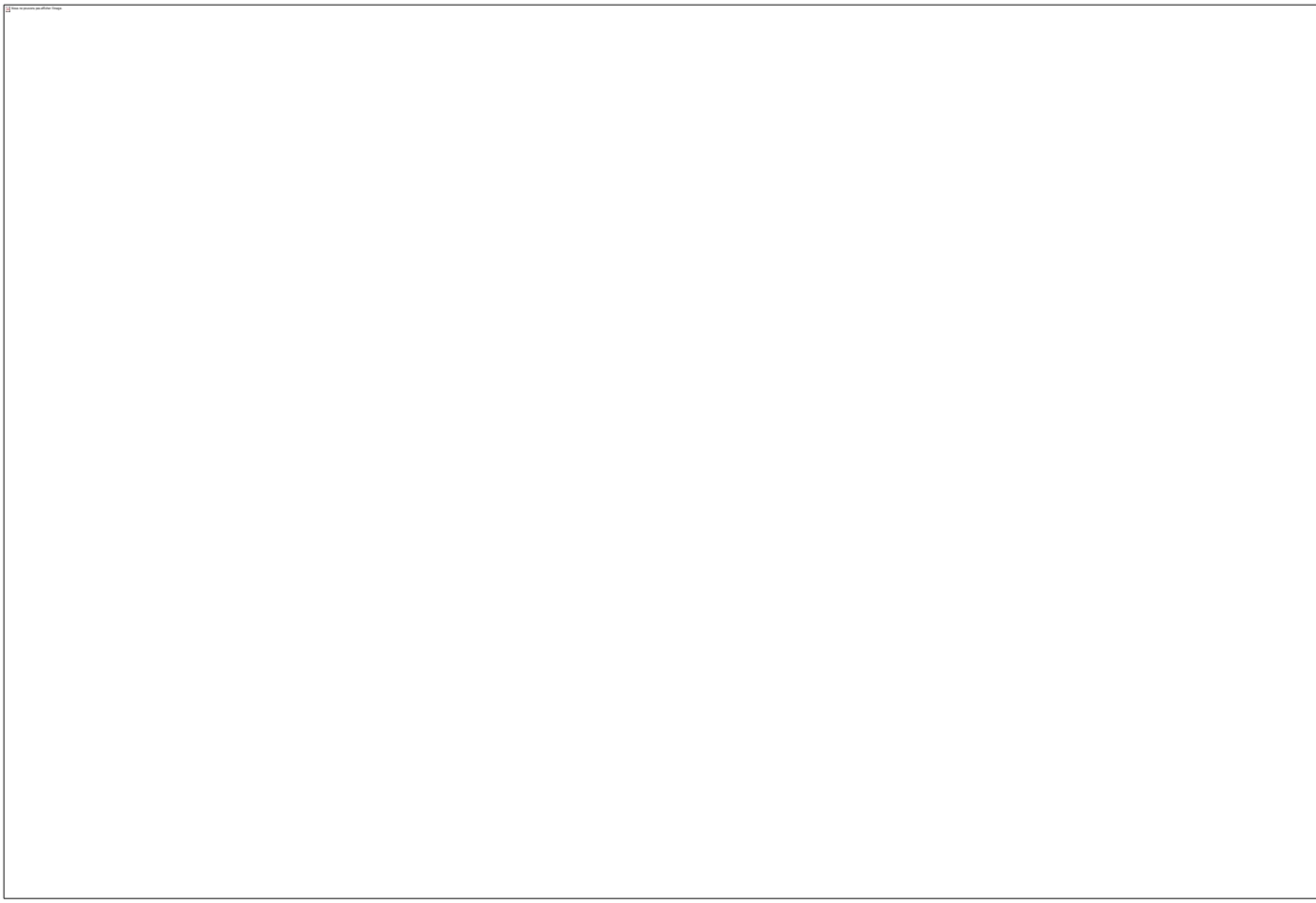
procedural pain, scarring of the cervix, and dysmenorrhea). Costs were converted to 2017 US$ using the medical consumer price index.

Conclusion

Of 30,978 eligible mid-adult women with conization, 81.0% had LEEP, 17.1% had CKC, and 2.0% had both CKC and LEEP). Few women were hospitalized (0.10%), with mean length of stay of 1.5 (0.80) days. The mean (sd) number of outpatient visits were 1.1 (0.4) for LEEP and 1.2 (0.4) for CKC. Post-operative complications occurred in 5.9% women overall (8.4% (CKC) and 5.3% (LEEP)). Mean all-cause costs were $3381, $5169, $2954, and $5443 for patients with any conization, CKC, LEEP, and both CKC and LEEP, respectively. Mean conization-specific costs were $1586, $2344, $1399, and $2671 for patients with any conization, CKC, LEEP, and both CKC and LEEP, respectively.

References

CKC is less frequent, more resource-intensive and expensive compared to LEEP. However, differences in patient characteristics could be related to type of conization procedure or predisposition for complications. HPV vaccination will reduce the incidence of pre-cancerous cervical lesions and should reduce the incidence and economic burden of conization.



00492

INCIDENCE AND TREATMENT-RELATED ECONOMIC BURDEN OF HPV-RELATED CERVICAL, VULVAR, VAGINAL, AND ANAL CANCERS IN THE US

32. Economics and modelling

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Background / Objectives

Human papillomavirus (HPV) infection is the most common sexually transmitted infection in the US. Persistent infection with high-risk types can progress to cancer. Recent estimates of the economic burden of HPV in the US are not available. The objective of this study was to estimate the incidence and treatment-related direct medical costs of cervical, vaginal, vulvar, and anal cancers attributable to high-risk types targeted by the 9-valent (9v) HPV vaccine (16/18/31/33/45/52/58) in US.

Results

We identified newly diagnosed cervical (ICD-O-3 histology codes 8010–8671, 8940–8941), vaginal (ICD-O-3 site code C52.9), vulvar (ICD-O-3 site codes C51.0–C51.9), and anal cancer cases (ICD-O-3 site code C21.0–C21.9) in all persons age 9 and above from the National Cancer Institute's SEER (Surveillance, Epidemiology, End Results) cancer registry in 2015. Annualized incidence rates were estimated from SEER*Stat software. Cancer sites were limited to squamous cell carcinomas (ICD-O-3 histology codes 8050–8084, 8120–8131). We applied published estimates of the proportion of each cancer site attributable to the 9vHPV vaccine-types to estimate incident cases attributable these types. Published lifetime costs of treatment for the cancers (two-year costs for cervical, vaginal, and vulvar cancer, and lifetime costs for anal cancer) were applied to estimate direct medical costs associated with the incident HPV-related cancer. Costs were inflated to 2015 dollars using US urban medical care consumer price index.

Conclusion

The 2015 annualized incidence rate per 100,000 person-years of cervical, vaginal, vulvar, anal (female), and anal (male) cases was 5.85, 0.29, 1.42, 1.78, and 0.95, respectively (Table 1). The economic burden (2015 dollars) of cervical, vaginal, vulvar, anal (female), and anal (male) cancer was $671 million, $50 million, $88 million, $129 million, and $71 million, respectively. Cervical cancer treatment costs accounted for 63% of the overall treatment costs of the 4 types of cancers. The economic burden of these cancers attributed to the 9vHPV vaccine types in 2015 dollars was over $1.0 billion.

References

Cancers attributable to 9vHPV vaccine types inflict substantial health and economic burden on society. The estimate of economic burden is conservative, as it does not include costs of prevalent infection (other than newly diagnosed cases), costs associated with screening and treatment of pre-cancers, indirect costs such as productivity losses due to cancer morbidity and mortality, and the burden of other HPV-related cancers (e.g., penile, oropharyngeal). Screening/HPV vaccination can help reduce the burden of these HPV-related cancers.

Table 1: Incidence and economic burden of HPV-related cancers

Age group	Incidence rate per 100,000 population for 9vHPV-related (16/18/31/33/45/52/58) cancers (2015)				
	Cervical cancer	Vaginal cancer	Vulvar cancer	Anal cancer - Female	Anal cancer - Male
09-15years	0.02	0.00	0.00	0.00	0.00
16-20years	0.03	0.00	0.00	0.00	0.00
21-25years	1.00	0.00	0.04	0.00	0.02
26-30years	5.47	0.00	0.09	0.00	0.17
31-35years	8.39	0.13	0.26	0.16	0.29
36-40years	10.28	0.05	0.46	0.35	0.41
41-45years	12.31	0.19	0.93	0.87	0.99
46-50years	10.86	0.36	1.73	2.41	1.47
51-55years	9.40	0.46	2.45	4.09	2.02
56-60years	9.58	0.68	2.52	5.97	2.63
61-65years	9.89	0.49	3.53	6.61	2.70
66-70years	8.21	0.91	4.04	7.06	2.75
71-75years	7.96	1.32	5.54	6.99	2.79
>75years	5.90	1.63	8.39	5.03	3.31
All ages	5.85	0.29	1.42	1.78	0.95
	2015 incident count for 9vHPV-related cancers (16/18/31/33/45/52/58)				
All ages	8,554	359	1,552	2,509	1,377
Economic burden for each cancer (million $; 2015 dollars)	$671.5	$49.5	$88.2	$129.2	$70.9
Total economic burden all cancers (million $; 2015 dollars)	$1,009.1				

33. Advocacy, acceptability and psychology

00081

HPV KNOWLEDGE AMONG EUROPEAN ADOLESCENTS AND THEIR PARENTS: RESULTS FROM A SYSTEMATIC LITERATURE REVIEW

33. Advocacy, acceptability and psychology

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Background / Objectives

The implementation of an HPV vaccination program has been recognized as a priority by Public Health Authorities. However, parental and adolescent attitudes towards HPV vaccination seem to have a major role to succeed and achieve a significant reduction of HPV-related burden of disease. Despite vaccines have shown to be efficacious, effective and with an acceptable safety profile, their level of acceptance and the vaccination coverage rates of the national HPV immunization programs differ widely across European countries (between 17-84%). To our knowledge, there is not a complete European systematic literature review summarizing factors influencing HPV knowledge and vaccine acceptability among adolescents and their parents.

The aim of this systematic review is to identify factors associated to parental and adolescents´ HPV knowledge in European countries where HPV vaccine is licensed. In addition, we summarize the results of studies evaluating parental and adolescents HPV knowledge and compile the measurement tools used in the published research studies in those countries.

Results

A systematic literature review was conducted through Pubmed, The Cochrane Library, Medline, EMBASE, Popline and the World Bank Library Network. Time period studied: January 1st 2006 to December 31st 2017

Conclusion

2,118 publications were identified. After excluding duplicates and studies not fulfilling inclusion/exclusion criteria, a subset of 70 studies were finally included in the systematic review. These studies have been performed in 17 European countries: United Kingdom: 27.1% Italy: 14.3%; Sweden: 11.4%, Netherlands 10.0%; Germany (5.7%); Greece, Hungary, Romania and Spain (4.3%); Denmark and France (2.9%) and Iceland, Finland, Belgium and Austria (1.4%). 18 of them reported data results on HPV knowledge. The number of respondents to any of the items related to knowledge in the surveys used across the studies was 161,483 adolescents and 75,830 parents. Overall, 53.1% of adolescents and 54.2%% of parents had heard about HPV; 34.0% of adolescents and 63.5% of parents knew diseases related to this virus; and 40.1% of adolescents and 77.3% of parents knew that HPV is a sexual transmitted infection.

Main socio-demographic factors associated to higher knowledge of HPV were gender (being female) in four 4 studies and vaccination status in 3 studies. No matter how investigators asked about HPV knowledge, it is consistently observed that the percentage of female adolescents (16.4%-57.54%) knowing about HPV is higher than the percentage of males (8.1%-48.08%)

References

HPV knowledge in parents and adolescents differs widely across regions and needs to be improved in order to increase vaccination coverage rates across Europe.

References

This study has been funded by Merck Sharp & Dohme Spain.

00083

HPV VACCINE ACCEPTANCE AMONG EUROPEAN ADOLESCENTS AND THEIR PARENTS: RESULTS FROM A SYSTEMATIC LITERATURE REVIEW

33. Advocacy, acceptability and psychology

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Background / Objectives

HPV is recognized as one of the major causes of infection-related cancer worldwide. Nowadays 3 HPV vaccines are available. Worldwide, HPV vaccination is part of the national vaccination programs of at least 80 countries. Moreover, HPV vaccination is recognized by WHO as a primary preventive intervention and recommends all countries to proceed with nationwide introduction of HPV vaccination. However, vaccine coverage rates differ widely within Europe and efforts to increase coverage rates and vaccine acceptability are still necessary.

The aim of this systematic review is to identify factors associated to parental and adolescents´ HPV vaccine acceptance and summarize the results of these studies, in European countries where HPV vaccine is licensed.

Results

A systematic literature review was conducted through Pubmed, The Cochrane Library, Medline, EMBASE, Popline and the World Bank Library Network. Time period studied: January 1st 2006 to December 31st 2017.

Conclusion

2,118 publications were identified. After excluding duplicates and studies not fulfilling inclusion/exclusion criteria, a subset of 70 studies were finally included in the systematic review. These studies have been performed in 17 European countries:

27% in UK, 14% in Italy and 11% in Sweden, 14 of them reported data results on HPV vaccine acceptance.

Up to 63 factors have been identified as having a statistically significant association with HPV vaccine acceptance in at least one of the studies: 17 factors related to “sociodemographic/family characteristics/ factual conditions” such as educational status, age of the respondent, family situation, nationality, religion, ethnicity, gender of the child and childhood vaccination. In 3 studies or more, parents and adolescents believed that vaccines were effective in preventing diseases, HPV related diseases were severe and HPV vaccination protected against cervical cancer.These beliefs were positively associated to HPV vaccine acceptance. In addition, when the source of information was a healthcare professional (specifically, a physician), the probability to accept HPV vaccination was higher. In contrast, doubts about HPV vaccine safety profile and the believe that vaccine may encourage child to have more partners or unprotected sex, were negatively associated to HPV vaccine acceptance.

References

There is still an important opportunity to improve HPV vaccine acceptance across Europe. Well balanced information offered by healthcare professionals seems to be critical to attend parents and adolescents’ hesitancy.

References

This study has been funded by Merck Sharpe & Dohme Spain.

00109

The association between maternal history of cervical cancer and HPV vaccination of children

33. Advocacy, acceptability and psychology

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Background / Objectives

HPV vaccination uptake remains low, with only 54% of U.S. children receiving at least one dose of the vaccine by age 13. Prior research has demonstrated that parental health beliefs and sociodemographic factors predict a child's HPV vaccination status. Less is known, however, about the relationship between maternal history of cervical cancer and children's HPV vaccination. The purpose of this study was to explore (a) whether mothers' personal history of cervical cancer predicted HPV vaccine uptake in their children and (b) whether this association may be mediated (i.e., explained) by greater perceived benefits of HPV vaccination.

Results

Data for this cross-sectional study were collected via an online survey conducted by Survey Sampling International. The survey targeted mothers or female guardians of children aged 9-13 living in the U.S. In a logistic regression model, we first estimated the effect of mothers' history of cervical cancer on maternal report of children's HPV vaccine uptake (i.e., at least 1 dose). Next, mothers' perceived benefits of HPV vaccination was included as a potential mediator of this relationship.

Conclusion

Of the 1,155 women (aged 18-81) providing data about cancer history, 70 reported that they had ever received a cervical cancer diagnosis. Children were 59% female, 41% male, and 32% had received one or more doses of vaccine. Maternal history of cervical cancer predicted greater odds of child vaccination (OR=2.65, 95% CI=1.87-3.74). Higher levels of perceived benefits of HPV vaccination also predicted greater odds of child vaccination (OR=2.78, 95% CI=2.34-3.30). When controlling for perceived benefits of vaccination, the association between maternal history of cervical cancer and child's vaccination status remained significant (OR=2.86, 95%

CI=1.68-4.87), suggesting that perceived benefits does not mediate the association between these two variables.

References

While mothers with a history of cervical cancer were more likely to vaccinate their children against HPV, this association does not appear to be due to greater perceived benefits of HPV vaccination. Mothers' HPV knowledge and/or perceived severity of cervical cancer (not measured in this study) could possibly contribute to this relationship. The current study builds on existing literature showing the link between HPV and cancer as a motivating factor in mothers' vaccination decisions. Clinicians and researchers may want to discuss HPV vaccination in the context of personal narratives about HPV-related cancers as a way of highlighting and humanizing the severe adverse effects of non-vaccination.

00557

Building Collaborations among HPV Vaccination Stakeholders: Examining the Impact of a National HPV Roundtable

33. Advocacy, acceptability and psychology

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Background / Objectives

In 2014, the National HPV Vaccination Roundtable was established by the American Cancer Society and the Centers for Disease Control and Prevention to increase the uptake and completion of the HPV vaccine in the United States. One of the primary goals of the Roundtable is to increase the collaboration between immunization and cancer prevention organizations. A detailed social network analysis is being conducted to understand collaboration among Roundtable members.

Presentation objectives include:

Outline the methodology used to assess the current collaborations
Review findings about existing collaborations, quality of collaborations, and where there is opportunity for development for enriching collaboration
Recommendations for how HPV Roundtables can impact collaboration

Results

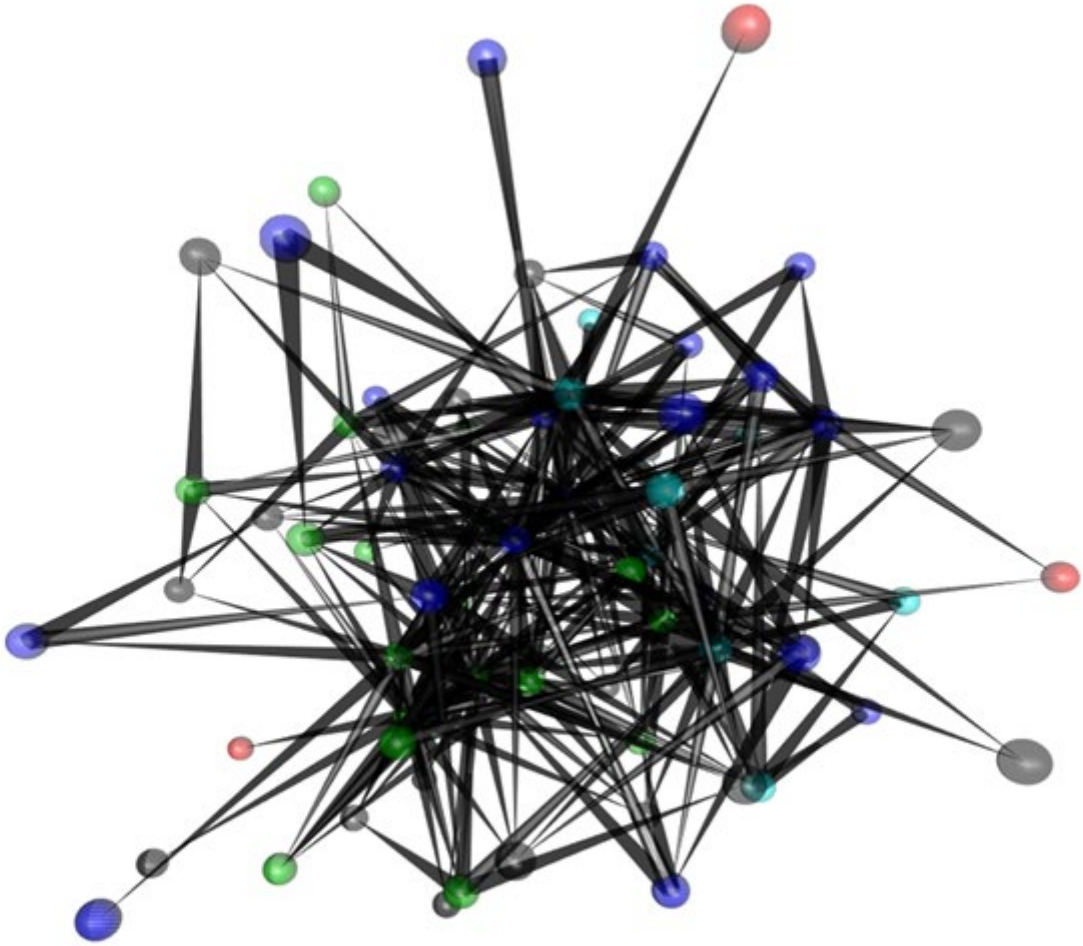
A detailed online survey was developed by a collaborative team based on existing assessments. The survey was distributed to 109 Roundtable members representing 72 organizations. Data was analyzed using SPSS, R, and NodeXL. Analysis included basic descriptive statistics and comparative analysis to examine the number of collaborations by type of organization (prevention or immunization) and by self-reported level of engagement on the roundtable. Social network analysis using R and NodeXL provided detailed information on model density, indegree, outdegree, and betweenness for each model. An overall network map was examined as well as network maps based on the depth of collaborations and the quality of collaboration scales.

Conclusion

A total of 74 respondents (67.9%) completed the survey, representing a total of 53 Roundtable organizations (73.6%). Data represented over 317 collaborative relationships. The network maps demonstrated that there were a few key organizations that had the highest degree of influence (indegree centrality) and are key information distribution points. Analysis by type of collaboration showed similar patterns of connection. Sociograms by type of collaboration found that organizations were more likely to collaborate with similar organizations than with other types. The average scale scores for quality and depth were relatively low and higher quality and deeper connections were found among similar organizations.

References

This project has demonstrated that there are a high number of connections among HPV stakeholders, however there is need for expansion of collaboration across types of organizations and strengthening of existing collaborations. There are key hubs for information distribution and connection among other partners. Cancer prevention organizations have the highest levels of collaboration and are the most central in the sociogram. Immunization and advocacy organizations have the greatest potential for future development and collaboration strengthening.



34. Health education

00257

WILLINGNESS OF ORAL HEALTH STUDENTS TO TRAIN AND ADMINISTER THE HPV VACCINE IN THE DENTAL SETTING

34. Health education

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Background / Objectives

A 153-item online survey was administered to United States students in 15 oral health programs. Secondary data analyses were conducted in SAS Version 9.4. Unadjusted and multivariable logistic regression were conducted and odds ratios (OR), 95% confidence intervals (CI), and p-values ($p<0.05$) were reported.

Results

A 153-item online survey was administered to United States students in 15 oral health programs. Secondary data analyses were conducted in SAS Version 9.4. Unadjusted and multivariable logistic regression were conducted and odds ratios (OR), 95% confidence intervals (CI), and p-values ($p<0.05$) were reported.

Conclusion

Data from N=306 students were analyzed. Receiving HPV vaccination information from professional journals or publications was positively associated with WT and WA ($p<0.05$). Agreeing that HPV vaccination recommendation (OR=1.95, 95%CI=1.14-3.35, p=0.015) and administration (OR=3.79, 95% CI=1.63-8.81, p=0.002) is in the dental professional's scope was positively associated with WT and WA even when adjusting for other factors (not my role to recommend, not enough time to discuss, not comfortable discussing, previous patient communication about HPV). Those who saw 21 or more patients a week (OR=4.47, 95% CI=1.14-17.58, p=0.032) and who agreed that HPV vaccine administration was in the dental professional's scope (5.9, 95% CI=2.27- 15.3, $p<0.001$) had higher odds of WA even when adjusting for other factors (not enough information, not my role, not comfortable discussing, previous communication about HPV).

References

Engaging dental providers in HPV vaccine education and vaccine administration can reduce HPV oropharyngeal cancers, which have now surpassed cervical cancer rates in the United States. Professional guidelines and endorsement of HPV vaccination from professional organizations are needed to engage dental providers in HPV vaccination efforts.

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00408

INSIGHTS ON HPV VACCINATION IN THE UNITED STATES FROM MOTHERS' COMMENTS ON FACEBOOK POSTS IN A RANDOMIZED TRIAL

34. Health education

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Background / Objectives

HPV vaccine uptake among adolescent girls in the USA remains below the national goal of 80%. Parent decisions to vaccinate daughters can be impeded by confusion, uncertainty, and misinformation about the HPV vaccine. This analysis summarized mothers' beliefs about vaccinating their adolescent daughters for HPV expressed in comments to posts on HPV vaccination in a social media campaign on adolescent health.

Results

Mothers with adolescent daughters from 34 U.S. states (n=880) were recruited to participate in a randomized controlled trial evaluating a social media campaign on adolescent health. Participants were recruited through Qualtrics survey panels or local efforts at the Tennessee study site. Eligibility criteria were: having a daughter aged 14-17, living in one of 34 states without a complete ban on indoor tanning for minors, using a Facebook account 1+ times a week, being able to read English, consenting to participate, completing the baseline survey, and willing to join the Facebook group. The campaign, implemented through Facebook private groups, included posts on HPV vaccination, as one of 7 general health topics. The experimental manipulation varied posts on indoor tanning versus prescription drug abuse prevention. Posts on HPV vaccination (n=16) and reactions and comments from mothers were extracted.

Conclusion

Mothers had a mean age of 43.1 years (sd=6.6); 6.5% were Hispanic and 86.6% white; and 63.1% reported that their daughter had been vaccinated for HPV (17.8%

receiving two shots and 31.5% three shots). HPV vaccination posts received on average 1.3 reactions (sd=2.8; range=0-11) and 3.3 comments (sd=8.8; range=0-35) from mothers. Comments often formed a dialogue among mothers. More than half of the comments (52.8%, n=28) were favorable, indicating that the daughter had been vaccinated and HPV vaccination reduced mothers' anxiety, HPV infection rates, and related disease risk. However, 45.3% (n=24) were unfavorable, citing safety concerns, lack of efficacy, unknown long-term consequences, inappropriate age for the vaccine, apprehension by other mothers, fears of vaccine tampering, lack of physician support, and sexual activity issues (e.g., plans to wait until daughter becomes sexually active; using vaccine to guard against unprotected sex). Some commented, mostly favorably, on the need to vaccinate boys.

References

Facebook comments indicated both support for and resistance to HPV vaccination by U.S. mothers. Reasons for not vaccinating girls were similar to barriers expressed in other research and reflected negative public information on HPV vaccination. Effective strategies are needed in social media to counter misinformation on and resistance to HPV vaccines.

36. Public health

00117

Issues Arising at Launch of Anti-HPV Mass Vaccination Campaign in 2018: Case of Estonia

36. Public health

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Background / Objectives

On 1st of January 2018, Estonia began an anti-HPV mass vaccination campaign at schools, using a nine-valent vaccine which had been selected and acquired through public procurement. The target group is 12-year-old girls.

Prior to starting vaccination, Estonian Health Board organized in Nov 2017 a nation-wide immunization training, at which, among other topics were the questions pertaining to the HPV vaccine and vaccination.

The state's favourable decision on vaccination (Q4 2017) and especially the launch of the vaccination program (Q1 2018) galvanised the anti-vaccination activists, who began to disseminate propaganda aimed at discrediting the HPV-vaccine through several media channels. Parents started contacting infectologists and gynecologists with concerned questions.

The Estonian Society for Infectious Diseases (EIS) and the Estonian Colposcopy Society (EKÜ) decided to support the nurses and organized nation-wide training for them between the 22nd of March and 4th of April 2018. 45% of school nurses attending these training seminars had previously participated in the training organized by the Estonian Health Board.

Results

Prior to the training, all participants were requested to submit questions which they had encountered during the launch of the HPV vaccination. As there were questions about communication with parents, the organizational aspects of the vaccination, and the vaccine itself, the questions were divided into 4 groups.

1. Safety of the vaccine
2. Necessity and efficacy of the vaccine
3. Organizational issues
4. Communication with parents/anti-vaccination activists

Conclusion

Communication issues constituted 58% of all problems and were divided as follows: communication difficulties with parents and/or anti-vaccination activists amounted to 64%, and the organizational issues of the vaccination amounted to 36%.

42% of all questions were directly related to the HPV vaccine, and these were divided as follows: questions about its safety amounted to 63% and efficacy to 37%.

References

1. The need for communication has substantially increased due to significant anti-vaccination movement both in the world and in Estonia.
2. Before including a new vaccine to calendar, as well as continually throughout the vaccination program, school nurses require continuous and specific training about the new calendar vaccine. At the same time it is important to raise awareness among parents, school management, media, and even the medical professionals (GPs, gynecologists) who should support the vaccination
3. It is crucial to maintain continuous communication between the school nurses performing the vaccination and the government institutions.

In order to achieve good coverage of HPV vaccination, EIS and EKÜ intend to continue organizing joint training for school nurses.

00401

Results from Ongoing Trials of Mobile Web apps to Improve HPV Vaccine Uptake

36. Public health

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Background / Objectives

In the U.S. uptake of HPV vaccine remains significantly below the Healthy People 2020 goal of 80% series completion, and this is particularly so for the young adolescent age range, when the immunogenic response to the vaccine is stronger. While a number of factors may account for this less than desirable vaccine uptake, parental concerns and misinformation about the efficacy and safety of HPV vaccine remain barriers to reaching public health vaccination goals. Physician and clinic-based interventions have shown some limited positive effect on vaccine uptake. However, parental barriers to HPV vaccination may ideally be addressed by digital interventions (in this case, smartphone applications) that are tailored to their concerns. Specifically, research indicates there is a great deal of 1) confusion and uncertainty about HPV vaccine and 2) concomitant misinformation about HPV vaccine, who it is meant for, and the conditions under which it is maximally effective. Reported here are the developmental research results and early trial findings from two smartphone web app projects, one focused on parents and adolescent girls (ages 11-14) and the other on parents and adolescent boys in the same age range. The objective of these investigations is to develop and evaluate a mobile web app to encourage HPV vaccination in New Mexico, an ethnically-diverse U.S. state.

Results

With funding from the Patient Centered Outcomes Research Institute (PCORI) and the National Cancer Institute in the United States, our team systematically developed a set of mobile web app tools to prompt the informed adoption of HPV vaccination. We used Diffusion of Innovations Theory and related research on Informed Decision Making to guide the iterative development of mobile apps for parents of young female and male adolescents.

Conclusion

Our presentation will review the website (Vacteens.org) and present development, baseline and preliminary efficacy trial data from the studies. Current ongoing randomized controlled efficacy trials with parents and their adolescent children in New Mexico clinics provide data to determine the impact of these mobile web apps on informed decision making and uptake for the HPV vaccine.

References

The progress and initial results of these ongoing research efforts have implications for reaching HPV vaccine uptake goals set by Healthy People 2020 in the United States. The presentation will focus on how mobile web-based interventions show promise for reaching HPV vaccine uptake goals. A mobile web app can make decision-making tools widely available on popular mobile platforms such as tablet computers and smartphones as well as personal computers.

00429

RECALL AND PATIENT NAVIGATION TO INCREASE CERVICAL CANCER SCREENING AMONG UN-/UNDER-SCREENED WOMEN IN A U.S. SAFETY NET HEALTHCARE SYSTEM: INTERIM RESULTS

36. Public health

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Background / Objectives

Patient reminders are a strategy recommended by the U.S. Community Preventive Services Task Force to increase cervical cancer screening. However, the utility of this approach among women who are past-due for screening (i.e., patient recall) is mixed. The purpose of this study is to evaluate the effectiveness of a centralized telephone-based patient recall and navigation intervention to increase clinic-based cervical cancer screening among patients enrolled in a large, urban public safety net healthcare system in the U.S. that serves a predominantly low-income racial/ethnic minority population.

Results

Women age 30-65 years who had not had a Pap test in ≥5 years (i.e., past-due for screening) were identified using the electronic medical record. A trained, bilingual (English/Spanish) patient navigator (PN) reviewed charts to assess additional eligibility criteria (i.e., no history of hysterectomy/cervical cancer, current healthcare plan coverage). Patients in the intervention group were contacted by telephone, educated about cervical cancer screening, and offered direct booking of an

appointment. Program effectiveness was assessed using an “intent-to-screen” approach by comparing Pap test screening rates between 01/18/18 and 05/31/18 among patients in the intervention group versus 220 randomly-selected historic controls.

Conclusion

During the specified period, the PN reviewed charts of 2,385 of 13,914 (17%) patients identified as past-due for screening. Of these, 30% (n=729) met the eligibility criteria for the intervention. Of 729 patients in the intervention group, 60% were reached by telephone. Among those reached, 41% scheduled a Pap test with the PN. Of the scheduled appointments, 31% were attended, 52% were not attended, and 16% were used to address another health concern. The overall Pap test completion rate among women in the intervention group was 14.7% compared to 8.3% among historic controls (absolute difference = 6.4%, $p<0.01$; incidence rate ratio = 1.8, $p<0.001$).

References

While Pap screening in a safety net healthcare system was increased 1.8-fold with the implementation of this telephone-based patient recall and navigation intervention, the absolute increase in Pap test screening remained small (6.4%). Of note, almost 70% of PN-scheduled Pap tests were not attended or used to address other health concerns. Further studies should explore strategies to eliminate barriers to appointment attendance among under-screened women, including potential alternatives to clinic-based screening (e.g., mailed self-sample HPV testing kits).

00510

Evolution of gender-neutral HPV vaccination in National Immunization Programs around the world

36. Public health

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Background / Objectives

Human papillomavirus (HPV) infection carries high disease burden in both genders, accounting for 5% of total cancers for males and females, the most common being oropharyngeal and cervical cancers. More countries are expanding HPV vaccination to males in National Immunization Programs. We aim to describe the evolution and status of HPV gender-neutral vaccination (HPV-GNV) worldwide.

Results

A comprehensive search using official government websites was conducted, complemented by a literature review (2008-2018) including publications in English, Spanish, and Portuguese describing male HPV vaccination programs.

Conclusion

Twenty-six countries with HPV-GNV were identified; 10 in North/South America, 13 in Europe, and 3 in Middle-Africa/Asia-Pacific. HPV vaccination for males was first recommended as routine immunization in the US and Puerto Rico in 2011. Czech Republic was the most recent to include males for the nonavalent vaccine in early 2018. Antigua directly adopted an HPV-GNV program in 2017. The target age for

male vaccination varies from 9 to 26 years according to each country's recommendation and predominantly focuses on adolescents. Delivery locations vary by country, including schools and/or medical centers. In 2018, Germany and UK are evaluating expanding HPV vaccination to males; Sweden is awaiting final decision. In addition to HPV-GNV programs, several countries have elected to include GNV only among men who have sex with men.

References

Increasingly, countries are expanding HPV vaccination to include males to improve population-level HPV infection control and directly prevent HPV-related disease in males. HPV-GNV has accelerated, with more than 50% of countries adopting such recommendations in the last 3 years.

00610

ADHERENCE TO HPV VACCINATION IS ASSOCIATED WITH PARTICIPATION IN CERVICAL CANCER SCREENING – A DANISH NATIONAL REGISTER-BASED COHORT STUDY

36. Public health

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Background / Objectives

Since the introduction of human papillomavirus (HPV) vaccination, concerns have been raised that HPV-vaccinated women would perceive themselves as fully protected against cervical cancer (CCU) and therefore not participate in CCU screening. Non-participants in CCU screening have a higher risk of mortality caused by CCU than participants. On this background we aimed to examine the association between HPV vaccination adherence and CCU screening participation to target future interventions to high-risk groups.

Results

In a national register-based cohort study, we included women born in 1993, representing the first birth cohort that was offered free of charge HPV vaccination in the Danish childhood vaccination program. Participants were residents in Denmark during 1.10. 2008- 31.12. 2016.

Exposure: Minimum one dose of HPV vaccine before end of 2015. Outcome: Minimum one cervical cytology after the age of 23 years before end of follow-up 31.12. 2016.

Primary outcome: Likelihood of non-participation in CCU screening among non-HPV-vaccinated women compared with vaccinated women. Socioeconomic factors were used to adjust for confounding.

Individual level information was collected from national health registries using the unique Danish civil registration number. Simple logistic regression was used to

estimate the association between participation in HPV vaccination and screenings. Multiple logistic regression was used to adjust for confounders.

Conclusion

A total of 24,841 women were included in the study population of which 21,687 (88%) were HPV-vaccinated. Among HPV-vaccinated women, 13,075 (60%) were screened compared with 1,496 (47%) of the non-vaccinated group. Non-vaccinated women were more likely not to participate in CCU screening than vaccinated women (adj. odds ratio (OR)=1.6;95% CI 1.5-1.7). This association was more outspoken among women from non-western countries (adj. OR=3.7; 95% CI 3.3-4.2) than among native Danes.

References

Non-participation in CCU screening among the youngest women may be a matter more of general behaviour and attitude towards health promoting offers than of interpretation of HPV vaccination as being fully protective against CCU. In order to overcome a social gab in the prevention of CCU, health promoting initiatives addressing certain groups may be beneficial. Especially, it seems necessary to understand how to target women with lower social status and women from non-western countries.

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PAPPILOMAVIRUS TRANSMISSION AND PREVENTION AND EFFECTIVE DISINFECTION

36. Public health

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Background / Objectives

Papillomavirus transmission studies have typically used cell-free virus prepared in organotypic raft culture, or recombinant pseudo-virus isolated from monolayer 293TT cells. Virus infection has been investigated by quantitating viral gene transcripts after infecting reporter cells. During natural in vivo infection however, virions are shed from the epithelial surface in squames, and the successful transmission/infection results in the new lesion formation.

Results

Viral transmission and survival was analysed using mouse papillomavirus (MmuPV) in a in vivo andin vitro model, in conjunction with in vitro infection of reporter cells using HPV16/18 raft virus. The output for the in vitro model for both MmuPV and HPV was quantitation of the E1^E4 transcript using RT-qPCR. The in vivo model utilised RNAscope to identify lesion formation microscopically and visual inspection for lesions macroscopically.

Conclusion

Similar to HPV16/18, MmuPV1 virus titre/infectivity can be quantified as virus gene transcripts by RT-pPCR (E1^E4) or RNAscope (E6E7) using HaCaT cells as a reporter cell. Virus titre/infectivity can be also quantified as periods of lesion formation in vivomodel with 5-6 log dynamic range. Up to 10 million virus particles can be produced from the surface layers of productively infected tissue and transmitted by direct contact, with an approximate one log drop in infectivity if transmission is mediated indirectly on fomites.Electron microscopy shows that MmuPV1 is E4 fibre-associated, and is stable following desiccation, with minimal loss of titre on fomites over 6 months. In contrast, cell-free MmuPV1 virion is not stable with loss of titre on fomites within 8 weeks.

References

MmuPV1in vitroand in vivoinfection models using natural virus produced from productive infected lesion are powerful methods to investigate HPV as it seems to mirror the characteristics of HPV making it a useful model to investigate transmission and susceptibility of HPV. Importantly, this model has demonstrated different viral shedding patterns (cell-free or in squames) can shows different virus infectivity especially following desiccation. Additionally, this model can be used to assess the safety of HPV disinfection and has been utilised to demonstrate the utility of OPA in stark contrast to other studies.