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.

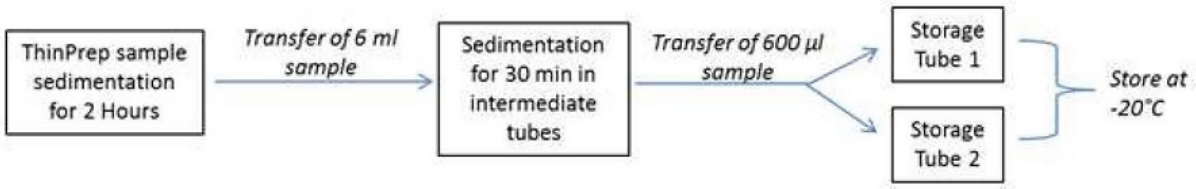
Conclusion

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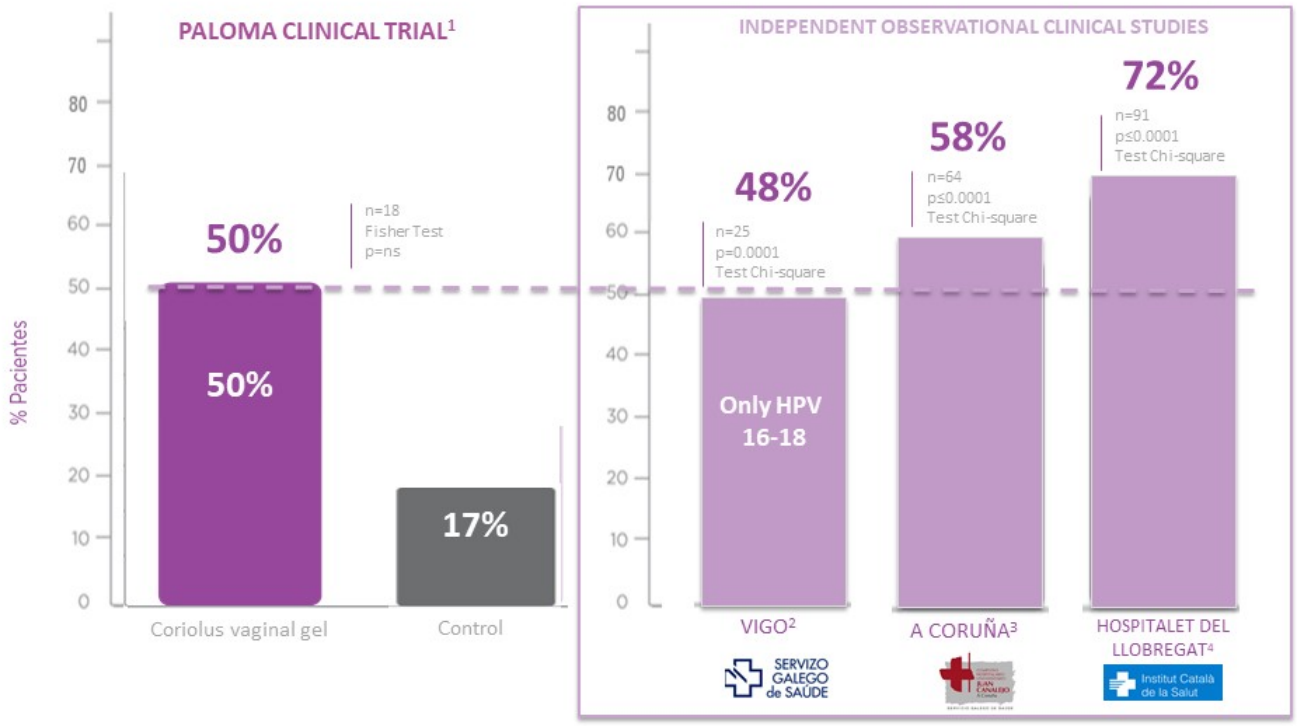
HIGH-RISK VPH CLEARANCE AT 6 MONTHS
(Paloma clinical trial vs Independent clinical studies)



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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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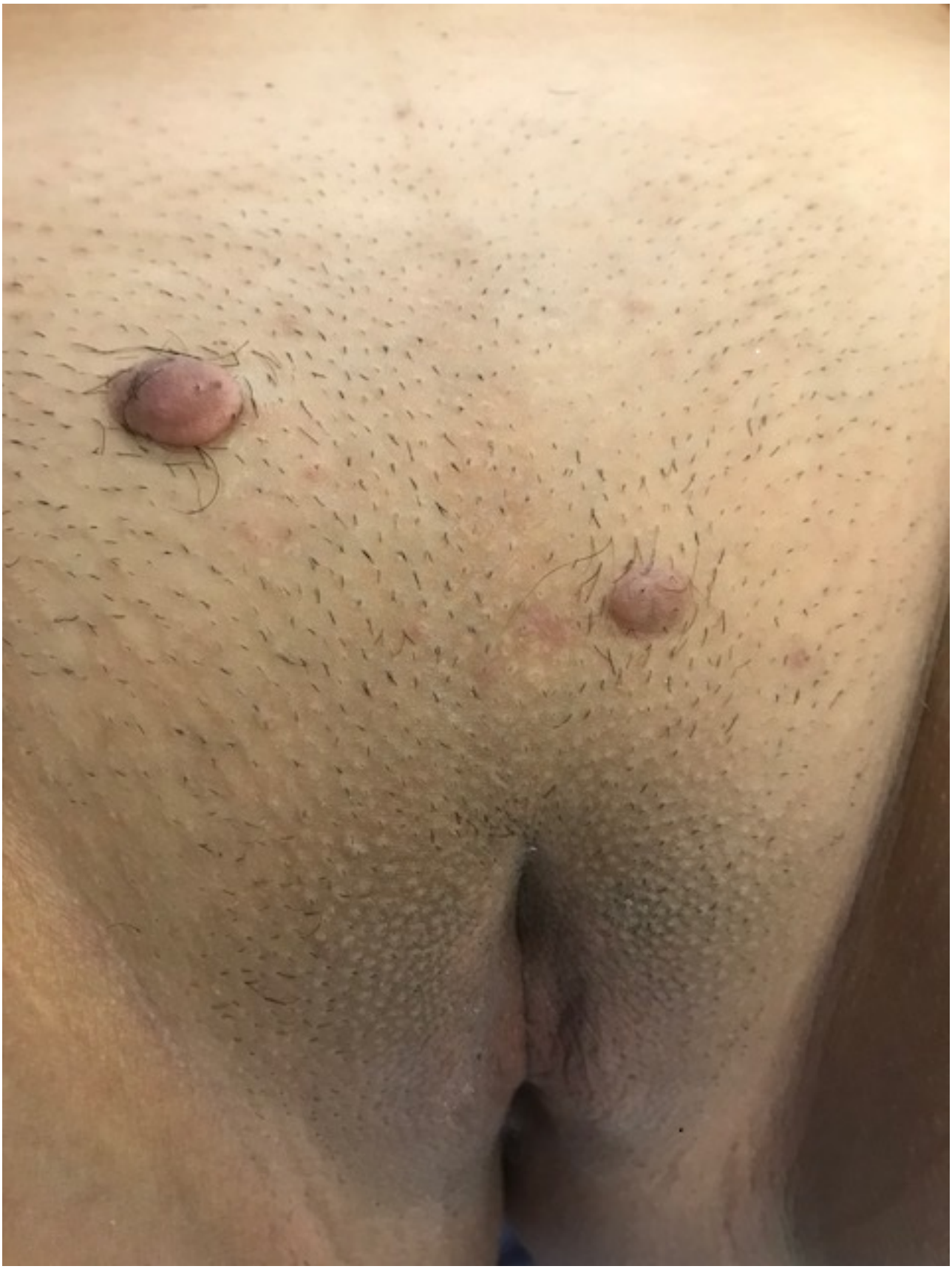

00507

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

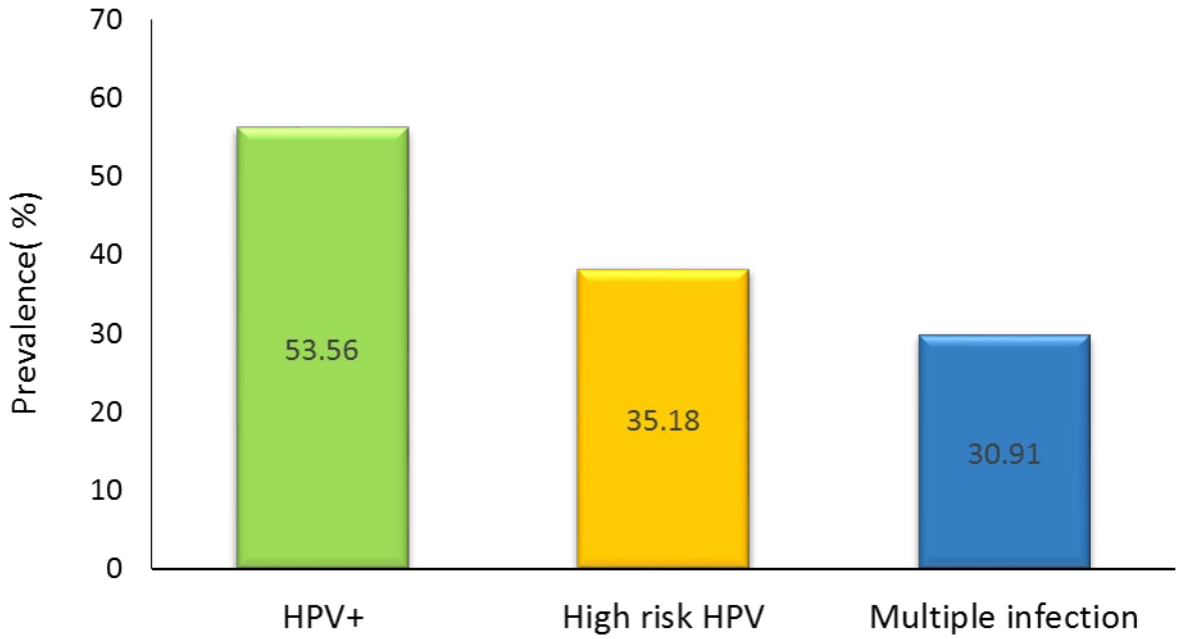
POP-Brazil Study is a cross-sectional nationwide survey who included sexually active women and men aged 16 to 25 years old. Participants were recruited in 119 primary care units by trained health professionals between September of 2016 and November of 2017. All participants answered a face-to-face interview 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

K.R. Dahlstrom

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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

JHSPH - Baltimore (United States of America)

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

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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]

[1]Leiden University Medical Center - Leiden (Netherlands), [2]Innsbruck Medical University - Innsbruck (Austria)

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

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Penn State College of Medicine - Hershey (United States of America)

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.

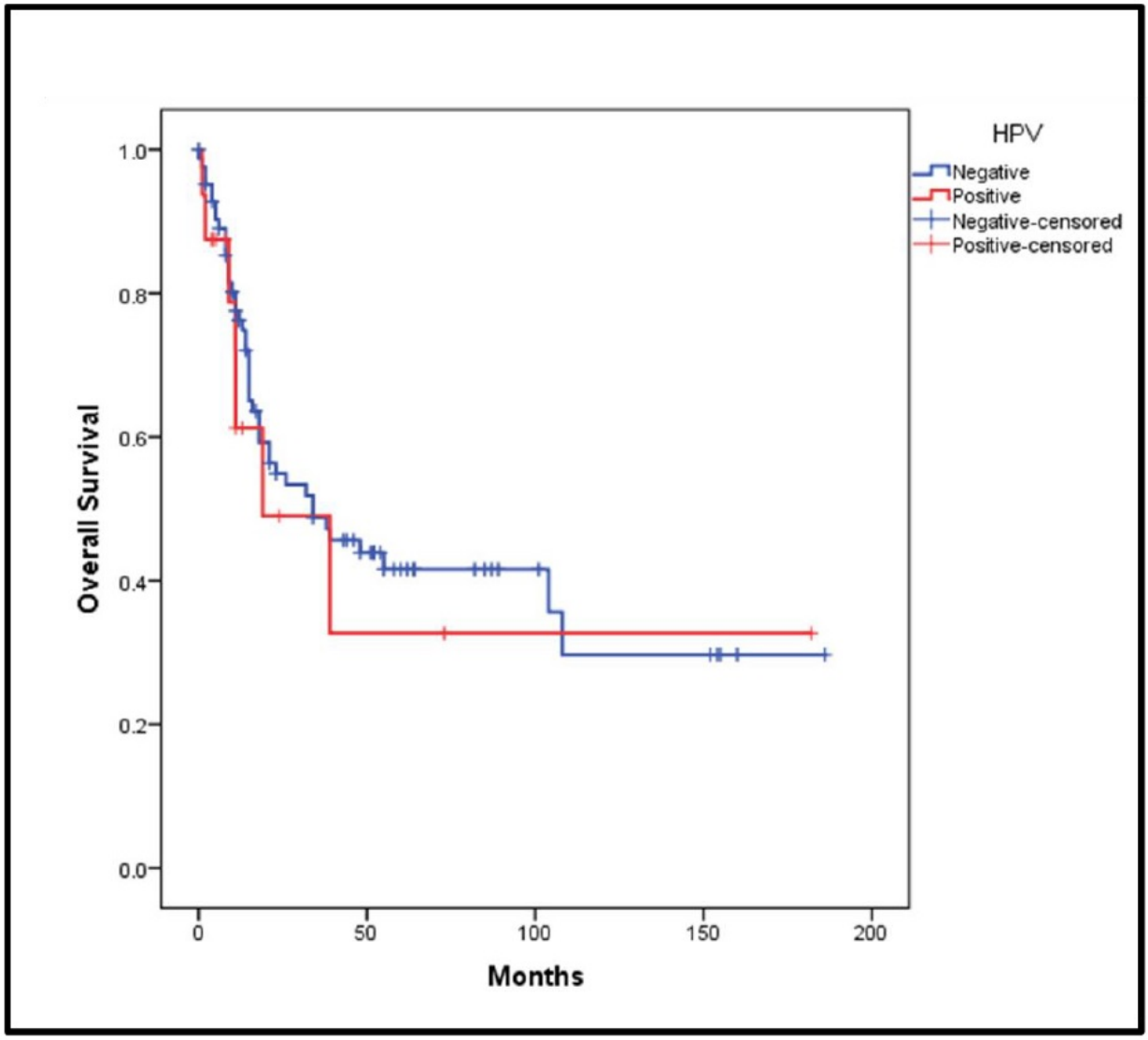
Conclusion

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.

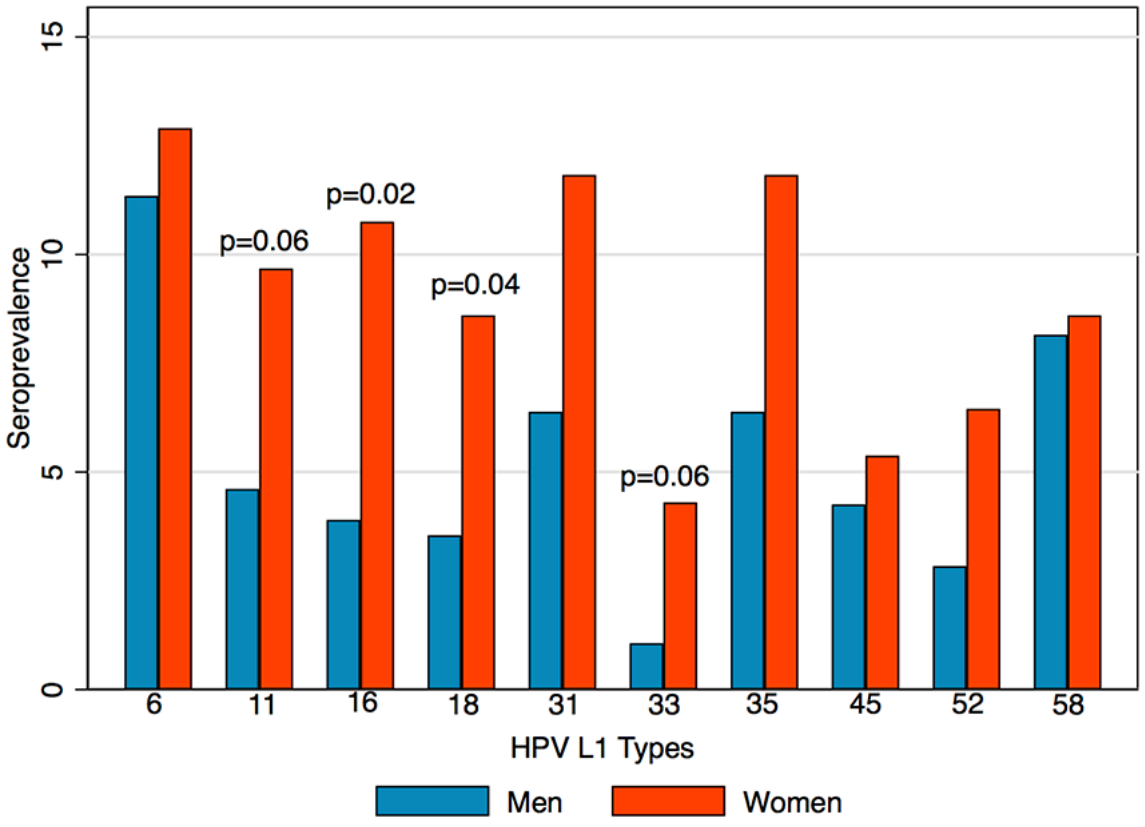
Conclusion

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.

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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)