EUROGIN 2019 ABSTRACTS

MAIN CONGRESS PROGRAM

WS 01 - Workshop HPV immunization - Part I

#0246

5 - HPV prophylactic vaccines

Follow-up studies with bi-valent and quadrivalent vaccines in Europe: impact on cervical diseases and elimination

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Background/Objectives: For over 12 years, the implementation and impact of the HPV vaccines has shown great promise in preventing HPV infection, low- and high-grade cervical disease, and anogenital warts. The call to action by the Director General of the WHO, Dr Tedros, for elimination of cervical cancer as a public health matter is both laudable and achievable. It can be achieved provided there is strong political will and successful implementation of vaccine programmes.

Methods: This presentation will focus on 3 specific regions of the world to highlight the different approaches to HPV vaccination, delivery, challenges and outcomes in high income countries where vaccination programs were first initiated. Population-based data will be presented demonstrating the considerable efficacy of the HPV vaccines throughout the world.

Results: Multiple studies and two systematic reviews show impact of HPV vaccination in real world settings. In a systematic review of outcomes after 4vHPV introduction, maximal reductions of 90% were reported for the four genotypes covered in the vaccine. In a recent systematic review and meta-analysis conducted to assess the population-level consequences and herd effects after female HPV vaccination programs, where coverage was greater than 50%, there were significant reductions in HPV16/18 pre and post vaccine periods of 80% in girls aged 15-19 years and of 65% for those aged 20-24 years, plus significant reductions (50%) in HPV types 31, 33, and 45 in the younger age group of girls suggesting cross-protection (Drolet et al., 2019). With respect to high-grade cervical disease, reductions in young women have ranged from 65-89% depending on age and uptake of vaccination (Australian Institute of Health and Welfare, 2018; Palmer et al., 2019).

Conclusions: The remarkable reductions in vaccine-targeted HPV genoprevalence, with subsequent reductions in associated short incubation outcomes in countries with high coverage vaccination underscores the potential to achieve the goal of cervical cancer globally.

References: Australian Institute of Health and Welfare 2018. Cervical screening in Australia 2018. Cat no CAN 111 Canberra:AIHW. 2018. Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019 Aug 10;394(10197):497-509. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, Cruickshank M. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ. 2019 Apr 3;365:l1161. doi: 10.1136/bmj.l1161.

MTC 02 - Revisiting the progress, practices and implementation of HPV based screening

#1039

12 - Molecular markers

DEVELOPING USEFUL BIOMARKERS FOR SCREENING AND TRIAGE

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Background/Objectives: Simplification of the process of cervical screening is a key aim of clinical research. Currently women who are either hrHPV positive or have abnormal cytology of ASCUS are subjected to triage by the alternative test and then if both hrHPV and cytology are positive they are referred for colposcopy and biopsy. Treatment is then decided mainly on the basis of subjective pathological interpretation of a cervical biopsy showing HSIL/CIN2+. This is a complex process that can cause distress and anxiety for the women involved. Furthermore the diagnosis of CIN 2 is particularly poorly reproducible and the outcome of CIN2 if left untreated is very variable with approximately 50% regressing. The immunohistochemical biomarker p16 has been available for almost 20 years as a marker of hrHPV E7 transforming gene activity, but its use as a single biomarker is very limited in cervical biopsy histopathology as described in the current LAST guidelines. The addition of further biomarkers, Ki67 and HPV E4 and the scoring of these biomarkers and p16 can elucidate some of the problems of p16 and provide a basis for defining in a standard reproducible manner CIN3 and the biological variability of CIN2. These immunohistochemical biomarkers do not avoid the use of biopsy. Over 100 biomarkers of hypermethylation of somatic and HPV genes have been identified and linked to carcinogenetic progression in the cervix. Some have been used on cervical cytological samples including self-samples. How these might be used in clinical practice to limit biopsy taking and provide reflex or even self-sampling triage of hrHPV positive women and a possible approach to clinical studies using methylation biomarkers is discussed.

Methods:

Results:

Conclusions:

HN 02 - Screening for HPV (I)

#0690

19 - Serology

Biomarker of choice: Serology. Understanding the strengths and limitations.

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Background/Objectives: Human papillomavirus type 16 (HPV16) infection is associated with multiple cancers, including oropharyngeal (OPC) and cervical cancers. Circulating HPV16 antibodies (Abs) are strongly associated with cancer risk and are being evaluated as potential biomarkers for screening. Multiple HPV-derived early antigens induce antibody responses that can be detected in plasma years prior to diagnosis and the probability of seropositivity increases closer to diagnosis. The clinical utility and impact of these biomarkers are not yet known. There are several current methods for measuring Abs to HPV-derived proteins, from laboratory-based diagnostics to rapid point-of-care assays. The performance of different serologic assays for HPV-associated cancers will be discussed. Developing models for screening individuals at risk will be reviewed.

Methods: n/a

Results: n/a

Conclusions: HPV serologic assays are potential biomarkers for screening and early detection of HPV-associated cancers.

SS 01 - Updating triage methods in HPV-based screening, an international experience

#0591

9 - HPV screening

o SS. Updating triage methods in HPV-based screening, an international experience / December, 4 / 13:30 - 15:00 / Title: The Italian algorithm: reflex cytology and hrHPV testing

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Background/Objectives: In Italy, HPV based screening has been introduced in 2013 with the receipt of the of the Italian HTA report recommendations by the Ministry of Health. The national prevention plan 2014-2019 set the objective for all the regional health services to complete the transition from Pap test-based to HPV-based screening. The Italian HTA report (Ronco 2012) used the same evidence collected for the European Commission guidelines (von Karsa 2015). The protocol adopted in the Italian screening programs, in fact, is one of those proposed by the European Recommendations: HPV-based screening should start at the age of 30 or 35, HPV-positive women should be triaged with cytology, if cytology-positive should be referred to colposcopy if negative to 1-year HPV retesting; only validated tests targeting HPV DNA of oncogenic virus types should be used. The rationale for this algorithm was to reduce the immediate colposcopy referral, maximising the advantage of sensitivity given by the HPV, so also women cytology negative but with two HPV positive tests were all referred to colposcopy.

Methods: Data from the implementation in routine programs (458,416 women screened in 2016 and followed up to 2018, www.osservatorionazionalescreening.)

Results: Data from ongoing programs confirmed the effectiveness of this strategy in identifying persistent CIN2+ lesions: detection rate is higher than with Pap test in the first round (4.8/1000 compared to 3.0/1000, but Pap-based screening was on a younger population, where higher prevalence is expected), while the detection in second round after a negative HPV test was much lower (below 2/1000, Del Mistro 2019). The main issue with this algorithm was an increase in referral to colposcopy, mostly due to very high persistence of HPV positivity at 1-year retesting (on average 54%). Furthermore, the positive predictive value of the colposcopy referral among women positive at retesting is very low (average 6.3%), this value was lower than what observed in randomized clinical trials and it is due to higher sensitivity of informed triage cytology compared to blind co-testing cytology used in trial, thus the yield of CIN2+ is higher in colposcopies performed immediately in women HPV+/cytology+ and lower in those referred to 1-year HPV retesting. A further observation emerging from the implementation was that total colposcopy referral, i.e. immediate and at 1-year retesting, is almost independent from cytology triage specificity (Ronco 2016).

Conclusions: All these observation oriented our research to very sensitive triage test in order to reduce the risk of missing important prevalent lesions that could progress in cancer in short time and thus making longer intervals safe for women HPV+/triage-negative women, allowing for a higher virus clearance.

References: Ronco G, Biggeri A, Confortini M, Naldoni C, Segnan N, Sideri M, Zappa M, Zorzi M, Calvia M, Accetta G, Giordano L, Cogo C, Carozzi F, Gillio Tos A, Arbyn M, Mejier CJ, Snijders PJ, Cuzick J, Giorgi Rossi P. Health Technology Assessment Report: HPV DNA based primary screening for cervical cancer precursors. Epidemiol Prev 2012;36 (Suppl 1):e1-e72 von Karsa L, Arbyn M, H, Dillner J, Dillner L, Franceschi S, Patnick J, Ronco G, Segnan N, Suonio E, Törnberg S, Anttila A. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus research 2015;1:22-31 Del Mistro A, Giorgi Rossi P, Frayle H, Pasquale L, Campari C, Ronco G, Zorzi M. 5-year risk of CIN3 after short-term HPV-DNA negativity in cytology negative women: a population-based cohort study. JOG 2019;126:1365-1371. doi:10.1111/1471-0528.15893. Ronco G, Zappa M, Franceschi S, Tunesia S, Caprioglio A, Confortini M, Del Mistro A, Carozzi F, Segnan N, Zorzi M, Giorgi-RossiP, and the Italian HPV Survey Working Group.Effect of the accuracy of tests for triaging HPV positive women on the overall screening performance. Eur J Cancer. 2016 Oct 15;68:148-155

HN 03 - Screening for HPV (II)

#0286

29 - HPV and oropharynx / Head and neck cancer

Implications of high-risk biomarker seropositivity: Bridging lessons from CIN to OPC

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Background/Objectives: Serologic biomarkers for HPV oncoproteins can identify individuals at risk for oropharyngeal cancer (OPC) with good sensitivity and very high specificity. However, it is unclear how these biomarkers might be translated into use for early detection of OPC. For cervical cancer screening, the current paradigm in the USA considers the absolute risk of disease (precancer or cancer) following different types of test results, such as cervical cytology or HPV testing. Then, management is recommended based on comparison of the individual's absolute risk with accepted thresholds for action. This talk will review the conceptual framework underlying risk-based guidelines for cervical cancer screening, and then use absolute risk data for serologic OPC biomarkers to consider how this framework might be applied in the setting of OPC.

Methods:

Results:

Conclusions:

WS 02 - Cervical cancer screening quality assurance - Part I

#0674

13 - Screening for women difficult to reach

BARRIERS IN ATTENDANCE AND ACCESS TO QUALITY ASSURED SCREENING

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Background/Objectives: Latvia has one of the highest cervical cancer incidences in Europe. Low attendance rate in the organized cervical cancer screening programme (OCCSP) and opportunistic screening, week involvement of primary health care, strong private sector in providing reproductive health care services are the most important factors that adversely influence the efficiency of the programme. The aim of the current study was to identify factors influencing the participation in the OCCSP.

Methods: A cross-sectional study in three general practitioners clinics in Latvia was carried out. Database of National Health Service of Latvia was used in order to identify women aged 25 - 70 who, during the last three years, had not participated in the cervical cancer screening programme. 523 of 992 women of screening population were included in the study. Results were compared between the three age groups (25-34 years, 35-49 years and 50-70 years of age).

Results: Most frequent answers to the question why women did not participate in the OCCSPwere - had not received invitation letter (41.5%), recent visit to gynaecologist outside the programme (22.2%), lack of time (20.8%). 466 of 523 women (89.3%) who did not have screening cytology were informed about the organised programme. 330 of 523 (63.1%) had ever received an invitation letter. More frequently (66/134, 49.3%) the participants aged 25-34 did not get the letter at all in comparison to the older respondents (65/177, 36.7% and 62/212, 29.2% in the age groups 35-49 and 50-70; p=0.001). Majority of study participants noticed that the most convenient way to receive the invitation letter still is by mail. Only 1.5% did not understand the content of the invitation letter. 68 of 212 (32.4%) 50-70 years old women did not have gynaecological examination for 3 years and more, compared to 6,4% in younger age groups (p<0.001). In contrast 84 of 134 (63.6%) younger participants attended gynaecologist annually, compared to the 50-70 years old respondents (69/212 participants, 32.9%), p<0.001. Possibility to give the smear with general practitioners (21.6%) and to get remainders from general practitioners (27.3%) could motivate respondents to participate in the organised screening programme.

Conclusions: GP should be more involved in the screening programmes - both in smear taking and reminding activities. Carefully managed invitation/reminder letters with scheduled appointments and self-sampling options offered to non-attending women can increase organised programme effectiveness.

MTC 04 - Recent developments in HPV research

#0844

2 - Epidemiology and natural history

New insights in cervical carcinogenesis and implications for screening

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Background/Objectives: The simplest model that accounts for cancer rates in screened and unscreened women defines the most reliable basis for HPV screening and triage protocols.

Methods: Our model assumptions 1. Each new HPV infection has a fixed probability (averaged over HPV types) of progressing to precancer before it disappears or becomes latent. 2. Precancer persists, conferring a constant lifelong cancer rate. 3. The interval from HPV infection to precancer plus the lag from cancer development to diagnosis averages 7.5 years, and is rarely less than 5 years. The age-distribution of HPV acquisition at entry to the ARTISTIC trial was assumed. The reduction in precancer prevalence, and hence cancer incidence, per screening round was modelled in English birth cohorts.

Results: English cervical cancer incidence rates since organised national screening began in 1988, including the unexpected large increase at age 25-29 since the screening age was raised from 20 to 25, were predicted with remarkable accuracy assuming 40% precancer elimination per cytology test. The model also explains the dependence on age and age at first intercourse of cancer incidence in unscreened women.

Conclusions: Our age-independent model of the relationship between HPV infection rates and cancer incidence rates contradicts several current assumptions. Screening at age 20 has little effect on cancer incidence at age 20-24 because of the diagnostic lag, not because it is ineffective in young women. CIN3 rates are misleading, because after the initiating HPV infection has cleared or become latent precancer is also often latent, undetectable by cytology and sometimes shedding HPV below the cut-off of standard HPV tests. Cancer incidence is therefore the only useful measure of precancer prevalence. 5-yearly HPV screening from age 20 instead of 25 would reduce cervical cancer risk below age 30 in unvaccinated English women from ~0.1% to 0.02% or less. The lifetime risk is ~3% without screening. Our conclusions Current opinion 1. Cancer risk in women with HPV level below the threshold for CIN3 detection Substantial Negligible 2. Model of cervical carcinogenesis on which to base screening policy Simple and age-independent, ignoring CIN3 diagnosis rates Complex and age-dependent to explain CIN3 diagnosis rates 3. Effect on cancer incidence up to age 30 of cytology screening from age 20 instead of 25 Prevents 40% of cancers at age 25-29 Negligible 4. Effect on cancer incidence up to age 30 of sensitive HPV testing from age 20 instead of 25 Prevents most cancers at age 25-29 Negligible

SS 02 - HPV and molecular testing of self-collected samples

#0402

12 - Molecular markers

Triage of women with an HPV+ self-sample: host DNA methylation and genotyping

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Background/Objectives: HPV self-sampling gains increased attention for use in cervical screening. However, an additional triage test is necessary for women with an HPV-positive self-sample to identify those 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.

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

Results: In both lavage and brush self-samples, significantly increased DNA methylation levels were observed in self-samples from women with CIN3 compared with HPV-positive controls. Also, methylation levels between self-samples and cervical scrapes were significantly correlated, with strongest correlation in women with CIN3+. 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-samples. Importantly, all self-samples from women with cervical cancer scored host cell DNA methylation-positive. 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.

Conclusions: 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.

#0296

10 - Self-sampling

COMPLIANCE TO FOLLOW-UP AMONG HPV-POSITIVE SELF-SAMPLERS

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Background/Objectives: An efficient self-sampling strategy requires high compliance to follow-up among HPV-positive self-samplers. Yet, compliance to follow-up has varied widely between studies. We assessed if high compliance to follow-up among HPV-positive self-samplers could be achieved without an intensive follow-up protocol.

Methods: The CHOiCE self-sampling trial included Danish women aged 30-64 years who were due to receive their second cervical cancer screening reminder (n=9,791). HPV-positive self-samplers (regardless of HPV type) were advised to attend cytology-triage at their general practitioner (GP) within 30 days. Test-results including follow-up recommendations were mailed to the women with a copy to their GPs. Compliance to follow-up was defined as attending for cytology-triage within 30, 60 or 90 days.

Results: Of the 905 self-samples returned, 118 (13%, 95% CI: 10.9-15.4%) were tested HPV-positive. Compliance with the follow-up cytology-triage sample at the GP within 90 days after a HPV- positive result was 90.7% (95% CI: 83.9-95.3%). More than half of the women (69.5%) attended follow-up within 30 days and were therefore compliant with the recommendation. Six women (5.1%) attended follow-up 91-180 days after receiving the test results, corresponding to an overall "long-term" compliance rate of 95.8% (95% CI: 90.4-98.6%).

Conclusions: High compliance to follow-up occurred, implicating that the chosen follow-up strategy was acceptable and successful. Key considerations for achieving high compliance include short follow-up time interval (30 days) and direct notification of the test-results to the women and their GPs.

HN 04A - HPV and oropharynx / Head & neck cancer (submitted papers)

#0573

29 - HPV and oropharynx / Head and neck cancer

SOCIODEMOGRAPHIC CORRELATES OF MORTALITY AMONG PATIENTS WITH HPV-POSITIVE OROPHARYNGEAL CANCER IN THE UNITED STATES

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Background/Objectives: Most studies on HPV-associated oropharyngeal cancer in the United States have relied on anatomic proxy in determining potential HPV-relatedness of disease rather than pathologically confirmed tumor status. However, determining actual HPV status is critical to accurately differentiate HPV-positive and HPV-negative cases for surveillance and clinical purposes. This study aimed to sociodemographic factors associated with mortality among confirmed cases of HPV-positive oropharyngeal cancer in the United States.

Methods: The Surveillance Epidemiology and End Results Program of the National Cancer Institute recently developed a custom dataset for oropharyngeal cancer cases with pathologically confirmed HPV status. Using this novel dataset, we included patients with oropharyngeal squamous cell carcinoma diagnosed from 2012 to 2016 with known HPV status. Among these patients, proportion of HPV-positive oropharyngeal cancer was calculated, and multivariable binary logistic regression estimated the association of sociodemographic correlates, including age at diagnosis, year of diagnosis, sex, and race/ethnicity, with developing HPV-positive disease. Fine and Gray competing risks proportional hazards model estimated the association between sociodemographic correlates with oropharyngeal cancer-specific mortality, after controlling for clinical covariates, including stage at diagnosis and treatment modality.

Results: While there were 16,850 oropharyngeal cancer patients diagnosed from 2012 to 2016, 37.6% had unknown/not applicable HPV status. Of the 10,520 patients with known HPV status, 7,902 (75.1%) had HPV-positive disease. Patients with HPV-positive oropharyngeal cancer were mostly male (87.6%) and non-Hispanic white (85.6%), with a mean age of 59.9 years at diagnosis. Five-year all-cause survival and cancer-specific survival for HPV-positive patients were 77.3% and 82.6%, respectively. Males had almost double the odds of developing HPV-positive oropharyngeal cancer than females (aOR = 1.91, 95% CI 1.70, 2.15), while racial/ethnic minorities were significantly less likely to develop the disease (aOR Hispanics = 0.63, 95% CI 0.53, 0.75; aOR non-Hispanic Asians/Pacific Islanders/American Indians = 0.60, 95% CI 0.48, 0.76; aOR non-Hispanic blacks = 0.33, 95% CI 0.28, 0.38) than whites. After controlling for clinical and other covariates, compared with whites, patients of Hispanic ethnicity who had HPV-positive oropharyngeal cancer had 34% increased mortality (sub-distribution hazard ratio [sdHR] = 1.34, 95% CI 1.01, 1.79). Mortality risk among blacks vs. whites also appeared increased, but did not reach statistical significance (sdHR = 1.31, 95% CI 0.97, 1.78).

Conclusions: This study estimates that three-in-four oropharyngeal cancer cases in the United States are HPV-positive, although as HPV status becomes more complete in national datasets, this estimate may need to be updated. Among patients with known HPV status, racial/ethnic minorities are less likely to develop HPV-positive oropharyngeal cancer, but they may be more likely to die from the disease. It is important to understand these sociodemographic correlates in surveillance and treatment of HPV-positive oropharyngeal cancer.

#0267

29 - HPV and oropharynx / Head and neck cancer

THE HPV-RELATED OROPHARYNGEAL AND UNCOMMON CANCERS SCREENING TRIAL OF MEN (HOUSTON STUDY): A PROSPECTIVE SCREENING TRIAL FOR HPV OROPHARYNGEAL CANCER

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Background/Objectives: IgG antibodies (Ab) to human papillomavirus type 16 (HPV16) are potential biomarkers for HPV-related malignancies including oropharyngeal cancer (OPC). In previous work, we showed 83% sensitivity and 99% specificity for identifying of patients with HPV16 OPC using a panel of HPV16 E antigens (Ag). We and others have shown rising titers up to 15 years prior to diagnosis. The goal of this study was to evaluate the utility of a panel of Ab to HPV16 E Ag in developing a screening strategy for HPV16 OPC among men.

Methods: The HOUSTON study (ClinicalTrials.gov identifier: NCT02897427) is a screening trial for HPV-related cancers being conducted at MD Anderson Cancer Center. The project is divided into a cross-sectional study and a longitudinal cohort study. The cross-sectional study will enroll up to 5,000 men aged 50-64 years. Serologic HPV16 and oral HPV16 status will be determined. The longitudinal cohort study will include a cohort of HPV16 Ab(+) and a matched cohort of Ab(-) men as well as oral HPV16(+) men selected from the cross-sectional study. Participants undergo screening for OPC including a head and neck exam and ultrasound of the neck every 6 months for up to 5 years as well as a one-time anal and penile cancer screen. IgG Ab to the HPV16 E Ag will be quantified using a custom RAPID ELISA assay. Ab status is based on a pre-defined binary logistic regression classifier.

Results: Of 528 men enrolled in the cross-sectional study, the median age was 57 years, 87% were non-Hispanic white, 72% had at least a Bachelor's degree, 73% had an annual income of >$100,000, and 69% were never smokers. Most (96%) reported having had any sex in their lifetime with a median number of 3 female (interquartile range [IQR], 1-12) and 14 male (IQR, 2-70) partners. Of the 93% reporting ever giving oral sex, the median number oral sex partners was 5 female (IQR, 2-10) and 20 male (IQR, 4.5-97.5). A total of 1.2% (6/498) were HPV16 Ab(+) and 9.3% (43/462) were oral HPV16(+). Forty-nine participants have been identified for the longitudinal study and 44 have been enrolled. Forty have undergone baseline, 34 6-month, 21 1-year, and 2 18-month clinical assessment. Although we expect to detect few cases of cancer, we have already diagnosed two cases of anal low-grade squamous intraepithelial lesions (LSIL) and one case of benign-appearing papillomatous lesions of the vocal cords. Loss to follow-up was 10%.

Conclusions: As expected, HPV16 E Ab positivity is rare among middle-aged men participating in a screening trial for HPV-related cancers. This biomarker panel may have potential in risk stratification for HPV-related malignancies.

#0069

29 - HPV and oropharynx / Head and neck cancer

DOWNSTREAM EFFECTS OF HPV INTEGRATION ON SURVIVAL IN HNSCC

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Background/Objectives: HPV-associated oropharyngeal cancer (OPC) has risen to epidemic levels in the US, where it recently became more prevalent than cervical cancer. Our objective is to identify markers for stratifying HPV+ OPC patients by risk, so that treatment protocols can be tailored to an individual patient, which would have substantial benefits. Our group was first to characterize the two main subtypes of HPV+ OPC, finding that one subtype is associated with expressed HPV integration events into the host genome and higher expression of the shorter isoform of HPV E6, E6*. Given that the tumor subtype differences can be explained by HPV integration, we sought to understand what effects the differences between them have on survival and metastasis.

Methods: Using 84 HPV+ head and neck tumors from the University of Michigan (n=18) and The Cancer Genome Atlas (TCGA) (n=66), we defined HPV integration status using RNAseq data to find HPV-host fusion transcripts, and tested for differences in overall survival by integration status using Cox-proportional hazards models adjusting for important covariates. Using the RNAseq data with clinical and additional molecular data, we identified three main integration effects: 1) increased relative expression of E6*, 2) decreased tumor infiltrating lymphocytes (TILs), and 3) a shift to partial epithelial-mesenchymal transition (pEMT). While it is known that reduced TILs negatively affect survival and pEMT increases the risk of metastasis, the effects of E6* are not well understood, with conflicting reports. Using a bioinformatics approach, we calculated an influence score for the protein activity of E6* in each tumor, and tested its relationship with survival, tumor mutational burden (TMB), and clinical variables.

Results: We found that patients with no identified HPV integration had better survival ($p=0.013$), and a lower percent of E6 expressed as E6* ($p=0.00068$). We identified 169 host genes whose expression is correlated with E6* ($q<0.05$), which were enriched for genes involved in OXPHOS ($q<10\text{-}17$). Using the E6* influence scores (derived from the 169 genes), we found that E6* is positively correlated with TMB (using TCGA; $p=0.0088$) and tumor size at diagnosis ($p=0.004$). Finally, E6* was found to be a significant predictor of overall survival ($p=0.0195$).

Conclusions: HPV integration has multiple effects that influence HPV+ OPC patients' survival. The negative impacts due to higher E6* suggest a potential clinical benefit to inhibiting E6 splicing. Future work is required to disentangle the effects of E6*, decreased TILs, and a shift in differentiation status on survival.

#0503

38 - Public health

ORAL CANCER SCREENING: EXPERIENCE OF BARRETOS CANCER HOSPITAL

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Background/Objectives: Head and neck malignancies are highly prevalent worldwide and it is estimated that over half a million cases are diagnosed annually with a significant morbidity and mortality rate. Head and neck cancers, specifically oral cavity carcinomas, although occurring in a location that is easily accessible for examination, continue to be diagnosed in advanced stages. Tobacco consumption and alcoholism are the main risk factors associated with the development of these neoplasms, although the increasing increase of HPV-induced oropharyngeal carcinomas has been documented, especially in developed countries. Primary prevention remains the best way to reduce the incidence of head and neck tumors and therefore minimize the morbidity and mortality associated with these tumors. Objective: Evaluate the survey of data on patients considered at high risk for the development of oral and oropharyngeal cancer examined and treated at the Prevention Department of Barretos Cancer Hospital from 2014 to 2017.

Methods: Retrospective study, with data collection from 2014 to 2017 of patients examined by visual examination of oral cavity and oropharyngeal and treated at the Department of Oral Cancer Prevention at Barretos Cancer Hospital (HCB) in the Hospital Ambulatory and Mobile Units. Sociodemographic and clinical information were collected including histopathological diagnosis, lesion topography, staging, type of treatment and clinical outcome. Data were stored in the RedCap® platform and submitted to descriptive statistical analysis.

Results: 8560 patients were evaluated from 2014 to 2017; of these, 5% (n = 442) were biopsied. The percentage of confirmed malignancies in the screened patients corresponded to 0.72%, 1.09%, 1.43% and 0.86% for the years 2014, 2015, 2016 and 2017, respectively, with a higher proportion of male patients, smokers, alcoholics and the oral cavity as the predominant tumor topography. 0.32% (n = 28) of the screened patients were diagnosed with potentially malignant oral lesions. Squamous cell carcinoma stands out as the main malignant neoplasm found (n = 87).

Conclusions: Screening for oral and oropharyngeal cancer are critical in the diagnosis of malignant and potentially malignant lesions of patients at-risk.

#0206

29 - HPV and oropharynx / Head and neck cancer

Diagnostic accuracy of HPV-DNA/p16INK4a double positivity in non-oropharyngeal head and neck cancer: results from the ICO international study

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Background/Objectives: Despite the HPV-attributable fractions (AFs) in non-oropharyngeal head and neck cancer (HNC) sites are much lower than in oropharyngeal cancers (OPC), the number of incident oral cavity (OCC) and laryngeal cancers (LC) worldwide far exceeds that of OPC, therefore even small HPV-AFs for these sites could potentially translate to a high absolute number of HPV-driven OCC or LC. For the diagnosis of HPV-driven HNC at non-oropharyngeal sites, tests or test algorithms have not been validated so far, neither the differences among non-oropharyngeal sites.

Methods: Formalin-fixed, paraffin-embedded cancer tissues of OCC, OPC, and LC were collected from pathology archives in 29 countries. All samples were subject to histopathological evaluation, DNA quality control, and HPV-DNA detection. HPV-DNA positive and a random sample of HPV-negative samples were subject to HPV E6*I-mRNA detection and p16INK4a immunohistochemistry. Three different cut-offs of nuclear and cytoplasmic staining were evaluated for p16INK4a overexpression: >25%, >50% and >70%. We assessed the accuracy of HPV-DNA/p16INK4a double positivity by estimating the sensitivity, specificity, odds ratios, and area under the curve (AUC) taking as gold-standard E6*I mRNA positivity, by HNC site, and compared the AUC.

Results: A total of 729 out of 3680 HNC with valid HPV-DNA results were also tested for p16INK4a and E6*I mRNA: 169 OCC, 431 OPC and 129 LC. HPV-DNA/p16INK4a double positivity showed a statistically significant higher AUC than p16INK4a positivity alone in OPC for >25% and >50% cut-offs (p-values 0.022 and 0.039, respectively), due to an increase of specificity, and marginally statistically significant for >70% cut-off (p-value 0.054). In OCC and LC, the increase of specificity was also observed, although not being statistically significant. Sensitivities of HPV-DNA/p16INK4a and p16INK4a alone were much lower for LC compared to OCC and OPC (56.3%-59.4% versus 78.7%-80.9% and 84.6%-85.5%, respectively) although specificities were equivalent. When restricting the analysis to HPV16 positive cases, a statistically significant higher AUC for HPV-DNA/p16INK4a double positivity than p16INK4a positivity alone was observed in OPC for any cut-off, including >70% (p-value <0.001), and marginally statistically significant in OC for >25% cut-off (p-value <0.070). Any improvement was observed in LCC, where sensitivity was still lower than 50%.

Conclusions: HPV-DNA/p16INK4a double testing may be useful for the diagnosis of HPV-driven OCC but not LC. Considering only HPV16 positive cases may improve the accuracy of the test for OCC. When assessing HPV-role on non-oropharyngeal HNC, a clear distinction between OCC and LC must be made.

#0153

12 - Molecular markers

HPV circulating tumoral DNA quantification by droplet-based digital PCR: a promising predictive and prognostic biomarker

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Background/Objectives: HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) constitutes a tumor entity with better prognosis and a distinct epidemiological profile, with specific genetic features, clinical presentations, and outcomes. Biomarkers are strongly needed to classify more precisely HPV-associated OPSCC with the aim to eventually consider de-escalation in the best prognosis cases. In the last decade, the liquid-biopsy approach using the detection of circulating tumoral DNA (ctDNA) released from tumor cells and detectable in blood growing interest including in head and neck cancers. HPV-related cancers are an ideal model to monitor ctDNA by detecting HPV oncogenes E6 or E7 particularly by ultrasensitive molecular assays such as droplet-based digital PCR (ddPCR). To determine whether pre-therapeutic assessment of HPV circulating tumoral DNA (HPV ctDNA) by ddPCR could constitute a predictive and prognostic biomarker for HPV-associated oropharyngeal squamous cell carcinoma (OPSCC), a mono-institutional prospective biomarker study on 66 patients with p16+/HPV16-positive oropharyngeal squamous cell carcinoma (OPSCC) was conducted in European Georges Pompidou Hospital, Paris, France.

Methods: Blood samples were collected at the time of diagnosis before any treatment. Optimized digital PCR assays were used to quantify HPV16 ctDNA. After a manual DNA extraction plasma using Qiaamp Minelute Virus Spin Kit (QIAGEN®, Hilden, Deutschland), ddPCR of HPV16 E6 gene was performed on a RainDrop Digital PCR System (RainDance Technologies, BioRad, Hercules, USA). To obtain absolute quantification of HPV16 ctDNA, data analysis was performed using the Raindrop Analyst software (FlowJo, Ashland, USA). The HPV16 ctDNA concentration was finally calculated in copies/mL.

Results: Forty-seven (71%) patients showed a positive pre-therapeutic HPV ctDNA at time of diagnosis. Interestingly, the quantity of HPV16 ctDNA at baseline, as assessed by ddPCR, was significantly correlated with the T/N/M status or stages according to the 2018 new staging criteria for High Risk human papillomavirus (HR HPV) related OPSCC from American Joint Committee on Cancer (AJCC). Moreover, all recurrences and the majority (83%) of death reported events occurred in patients with positive HPV16 ctDNA at baseline. Finally, when post-treatment blood samples were available (n=6), the kinetic of pre-/post-treatment HPV16 ctDNA was clearly associated with treatment success or failure.

Conclusions: HPV ctDNA monitoring by ddPCR could constitute a useful and noninvasive dynamic biomarker to select HR HPV-related OPSCC patients eligible for potential treatment de-escalation and to monitor treatment response.

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WS 02 - Cervical cancer screening quality assurance - Part II: Interactive session with selected papers

#0400

13 - Screening for women difficult to reach

Cervical Cancer Prevention and Control Program in Nepal: A Success or Failure?

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Background/Objectives: Cervical cancer is the commonest of cancer and the leading cause of cancer death among women of developing countries. It is the most common cancer among women of Nepal.In view of the limited surveillance, cervical cancer has been found to account for 21% of all cancer in women of Nepal according to national cancer registry report (2003-2012).The difficult geographical terrain, resource strained heath economy and inability of the majority to bear out of pocket expense it seems difficult to suggest one screening method best over another. Thus It seems to be high time for Nepal to adopt an affordable and achievable target for the utilization of suitable cervical cancer screening methods creating own comfortable model to control the burden This is a presentation of the course followed for cervical cancer screening program development in Nepal and to discuss for better future screening model based on the finding of one of the study conducted in remote hard to reach terrain of Nepal

Methods: 1)Review of the national cervical cancer prevention program of Nepal.A course from initiation of the cervical cancer screening and prevention program to the national immunization program against HPV 2)Cross-Sectional Study of different cervical cancer screening methods and follow up modality in year 2018 and 2019 in Khumbu Pasang Lhamu Rural Municipality of Solukhumbu district and Screened female were 468 in year 2018 and 107 in year 2019 468 women were screened with Visual Inspection Acetic acid(VIA) and HPV test. HPV samples transfer to central laboratory . VIA positive cases were documented with photograph by smart-phone and offered treatment with thermo-coagulation as a single visit approach (SVA). In the year 2019 Self collected samples of 107 were tested with HPV test using Xene Expert, set in the same locality

Results: Development of complete Training package and Introduction of VIA in nursing curriculum.Development of Referral linkage model with improved service using mobile app and social media. Country heading for SVA and HPV vaccination with bivalent vaccine. Study result,Out of 468 screened,VIA positive were 18(3.8%) cases where as HPV positive were 42(9%) cases in first cohort of 2018 whereas in 2019,107 were screened (HPV test only), 16(14.95%) were positive for high risk HPV. For the HPV types,17 harbours single genotype commonest HPV-58. 13 cases with 2 HPV and commonest 16, 52 and 18, 35 type. And 7 cases with 3 types and 2 with more than 3 types of High risk HPV. In 2019-Self collected samples, 100% were satisfied with the process rather than examined by health worker. Found that HPV 18 & 45 in 1case HPV 16 in 3 cases, HPV others (11 types) in 10 cases and Mixed were in 2. In the analysis of Relationship between VIA & HPV test result Out of 42 HPV positive cases only 9.5% were identified as VIA positive with visible lesion whereas remaining 90.5% were without lesion similarly 426 negative HPV cases, 3.3% recorded as VIA positive

Conclusions: Single visit approach with VIA and cold coagulation seems acceptable and feasible.But Comparing VIA with HPV results, false VIA positive seems high. So shifting to self collected sample HPV test following the single visit approach with cold coagulation as a treatment option can be the best model even for the most difficult and hard to reach terrain of Nepal.A question it raise Are we in the right path of introducing Bivalent/Quadrivalent HPV vaccination in Nepal looking at the prevalent HPV type?

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#0112

13 - Screening for women difficult to reach

EVALUATION OF CERVICAL CANCER SCREENING UPTAKE AND RISK FACTORS KNOWLEDGE: HEALTH BELIEFS MODEL (HBM)

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Background/Objectives: Background: Even though 20 million women are eligible for cervical screening in Ethiopia only less than 1% of women are screened. Part of the explanation for the low uptake of cervical cancer (CC) screening could be rooted women`s health beliefs and inadequate knowledge of risk factors. Objectives: To assess women health beliefs on CC screening and CC risk factors knowledge who visited Sister Aklesia Memorial Hospital (SAMH) for any medical reasons in Adama town, Oromia, Ethiopia.

Methods: A cross sectional study was conducted and a total of 412 women participated between September and December 2017. The health belief model is used to study factors influencing Ethiopian women's participation in cervical cancer screening.

Results: The average age of women was 44.6 years. Among 28 women who were visited health facility for the purpose of screening, thirteen (3.2%) had underwent screening test either of VIA or Pap test. Association between women's education and household income with health facility visit for the purpose of screening were found statistically significant ($p<0.05$). Women (384/412) were not visited clinics for the purpose cervical cancer screening because of perceived health beliefs where "douching every day" could prevent CC; "uncomfortable if a man did the procedure"; "no self-sampling device available", and no single "see and treat" visit approach existed were the main barrier factors. Women believed that they would not be susceptible of cervical cancer when they were not have sex with many partner ($p<0.05$) and didn't have symptoms ($P<0.05$). Significant number of women ($p<0.05$) didn't consider abnormal CC screening tests without treatment can lead to cervical cancer.

Conclusions: Understand deeply Ethiopian`s women health beliefs and barriers for cervical cancer screening is important, and changing their social structure and living condition could improve screening uptake through health education and awareness program at all level.

#0238

13 - Screening for women difficult to reach

CONTINUOUS QUALITY MONITORING LEADS TO THE IDENTIFICATION OF NON-PARTICIPATION, IRREGULAR PARTICIPATION AND INADEQUATE FOLLOW-UP AS ISSUES FOR IMPROVING EFFECTIVENESS OF CERVICAL SCREENING

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Background/Objectives: An organised cervical cancer screening program was set up in 2013 in the Flemish Region for women aged 25 to 64. On demand of the Flemish Agency for Care and Health, the Belgian Cancer Registry (BCR) yearly monitors the program in collaboration with the Centre for Cancer Detection to identify barriers impeding optimal functioning of screening.

Methods: Besides cancer diagnoses, BCR collects all results of cervical samples in a central registry, completed with administrative data from health insurances. BCR is crucial due to the centralisation of these data and the possibility of individual linking using a unique patient identifier. By linking these databases with a Flemish population registry, BCR calculates several quality indicators such as detailed screening coverage, regularity of participation and follow-up rate of positive women.

Results: In 2017 the overall coverage was 62.2%. It is highest between the age of 30 to 49 (>65%) and decreases from 50 years on to 48.8% for the oldest group 60-64 years. Surprisingly, during the period 2013-2017 coverage decreased from 64.8% to 61.2% for the youngest group of 25-29 years. 16.3% of the women had no screening at all since 2008, with the highest % of non-responders in the oldest age group (29.1%). Old data retrieved from health insurances showed that about 4% of the age group 60 64 appeared to have had a hysterectomy before 2002. By adding this data coverage rose for 2017 to 52.8% for age group 60-64 and to 63.6% for all ages. Tailored communications will be sent to non-responders. 6% of the population is overscreened. Despite participation in 2015 or 2016, these women had a screening smear in 2017 and are out of medical follow-up. The screening frequency of women eligible in 2017 with at least 1 participation in 2012 to 2017 was evaluated. 8.8% had in the 6-year period 1 (first) participation; 20.4% had two participations with two calendar years in between as recommended. All other women (70.8%) participate with either more or less time interval. This shows that irregular screening seems to be an issue too, besides overscreening and non-participation. The follow-up rate of abnormal screening smears was 81.4% in 2017. In 2018 a fail-safe mechanism was set up. For all women with a high grade lesion without follow-up within 12 months, the doctor who took the sample is notified. Fail-safe lists are drawn up 4 times a year. Up to know 4 lists have been drawn up containing in total 510 women eligible for fail-safe.

Conclusions: Quality indicators reveal the weaknesses in the screening program. They can be directly translated into policy decisions to optimize the coverage and improve the follow-up rate.

#0262

13 - Screening for women difficult to reach

Interventional study evaluating cervical cancer screening strategies for women in precarious conditions in France

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Background/Objectives: Médecins du Monde (MdM) beneficiaries live in extremely precarious conditions, have limited access to gynecological follow-up and cervical cancer screening (CCS) and are particularly exposed to papillomavirus (HPV) infection. The study aimed to evaluate two CCS strategies after a cervical cancer prevention consultation: Pap Smear test (PST) versus self-sampling HPV-test (PST in case of positivity).

Methods: Interventional, multicenter, comparative and randomized study. Implementation period: Mars 2017- December 2018. Inclusion criteria: women from 25 to 65 years old in four MdM programs (Healthcare and Referral Clinics, mobile clinics in informal settlements and harm reduction towards sex workers) and four locations (Lyon, Bordeaux, Rouen and Paris). Exclusion criteria: "screening up to date", "total hysterectomy" or "no sexual intercourses". Evaluation criteria: proportion of women with complete screening tests (negative HPV test or PST done) and proportion of cytological abnormalities detected (≥ASCUS). Statistical analysis: logistic and Cox regression.

Results: From 799 participants, 112 were excluded (14.0%). Mean age was 41.0 years. Women were mainly from sub-Saharan countries (62.7%), in irregular situation (73.4%) and without health coverage (59.3%). 22.4% have never visited a gynecologist and 53.4% had never done a PST. 23.8% were sex workers. 304 women were assigned to the control arm (PST) and 383 to the intervention arm (HPV+PST). The proportion of screening completeness was 39.5% in the control arm and 71.3% in the intervention arm (RR = 1.80 (1.55-2.10)). The CCS was completed in 18.6 days in the control arm and 9.5 days in the intervention arm (HR = 2.48, (1.99-3.08)). The proportion of cytological abnormalities detected was 2.0% in the control arm and 2.3% in the intervention arm (OR=1.20 (0.42-2.40). There was a high proportion of lost to follow-up after PST referral (60.7% and 63.0% in control and intervention arms, respectively).

Conclusions: Self-sampling HPV test approaches precarious population to CCS, improve its completeness and optimizes PST performance. Nevertheless, it is essential to reduce the number of lost to follow-up, especially after a positive HPV-test result.

#0534

13 - Screening for women difficult to reach

LOW CERVICAL CANCER SCREENING PROGRAMME COVERAGE - HOW TO MOTIVATE NON-ATTENDERS OF DIFFERENT AGE GROUPS?

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Background/Objectives: Latvia has one of the highest incidence and mortality rates of cervical cancer in Europe - 19.2 morbidity and 10.2 mortality cases per 100 000 women in 2017.1 Organized cervical cancer screening was introduced in Latvia in 2009, however response rate for screening is very low - annually about 26%.2 The aim of this study was to analyse the factors, that may increase cervical cancer screening coverage in the different age groups.

Methods: A cross-sectional study was performed in the three general practitioners' clinics from 01.01.2017 to 30.06.2017. National Health Service database was used to identify women aged 25-70 who, during the last three years, had not participated in the organized cervical cancer screening programme. The results were compared between two age groups. The study was approved by the Ethics Committee of Riga Stradins University. Statistical analysis was performed using IBM SPSS 23 software and MS Excel.

Results: According to our data a total of 523 women were surveyed. 311 (59.5%) women were younger than 50 years and 212 (40.5%) women were over 50 years. The most frequent factors, which could motivate younger women of reproductive age to participate in the organized screening programme were - possibility to give the smear with their own gynaecologist (50.5%), improvement of availability of gynaecologists near the living place (26.1%) and reminders from general practitioner (25.7%). Compared to older participants, younger women more often mentioned that more extended information regarding cytological examination and expected results (11.9% vs 8.0), p=0.185 and more information about the organised cervical cancer screening programme in Latvia are required (11.6% vs 9.4%), p=0.094, whereas the older ones would like to have screening cytology with general practitioner (32.1% vs 14.5%), p<0.001 and shorter waiting times (22.6% vs 18.6%), p=0.456.

Conclusions: It is crucial to involve more primary care professionals in the organised cervical cancer screening programme to increase coverage. More information should be provided about the cervical cancer screening programme - aims and benefits of prophylactic gynaecological examinations in all age groups of screening population should be outlined. Cytological tests should be provided only as a part of organised screening programme.

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SS 03 - HPV vaccination in adults

#1038

5 - HPV prophylactic vaccines

INTRODUCTION: HPV VACCINATION IN ADULTS

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Background/Objectives: The control of infectious diseases has typically involved three levels of intervention: 1) if feasible, reduction of exposure of the population to the infectious agent; 2) individual protection by vaccination; and 3) secondary interventions to diagnose and treat the cases. In the HPV model, vaccines are achieving great success in programs that initially focused on vaccination of adolescent girls; programs are now slowly expanding to boys and extending catch-up vaccination to ages 18-26 years with licensing now proposed either through age 45 years (i.e. in the USA) or without upper age limits (i.e. in the EU). In all instances, vaccinated cohorts are already experiencing significant reductions in infections and related lesions (point 2). Likewise, screening programs using novel HPV technologies are highly effective in reducing cancer incidence and mortality (point 3). Further impact could be achieved by focusing on the options to reduce exposure of the population to HPV (point 1). In fact, the social reservoir of HPV and the source of the high prevalence are known and include the approximately 12% of women with HPV-positive test results and normal cytology and the 40% of HPV-positive male carriers, as well as the sexual behavior-driven high risk groups (e.g. patients at STI clinics, gender neutral commercial sex workers, HIV carriers). Several research lines are exploring whether HPV vaccination of these reservoirs (i.e. the HPV-positive women identified at screening) would indeed reduce HPV transmission, thus boosting the herd effect already observed in several population based vaccination programs. It is postulated that vaccine-induced antibodies would coat the virions of the HPV carrier, thus shedding less infectious viral particles. Further, expanding the indication to vaccinate all adult women irrespective of their HPV status could reduce transmission, offer greater protection to the individuals if challenged with HPV, notably if broad spectrum vaccines are used, and potentially reduce their screening requirements and its consequences (diagnostics and treatments).

Methods: N/A

Results: N/A

Conclusions: N/A

References: N/A

#0636

5 - HPV prophylactic vaccines

HPV VACCINATION PROTECTS AGAINST HPV INFECTION AND DISEASE IN SEXUALLY ACTIVE ADULTS: A REVIEW OF QUADRIVALENT HPV VACCINE CLINICAL TRIALS

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Background/Objectives: The quadrivalent HPV (qHPV) vaccine clinical trial program included sexually active females who may have had exposure to HPV. As most sexually active individuals are infected with HPV during their lifetime, participants enrolled on the qHPV clinical trial program would have been infected with at least one HPV type. As participants were not excluded based on baseline HPV status, the per-protocol efficacy (PPE) analyses for each vaccine HPV type (HPV6/11/16/18) included participants infected by other HPV types included or not included in the vaccine. During the clinical trial program, the efficacy of the qHPV vaccine in females aged 16-45 years was consistently high. The qHPV vaccine is prophylactic and no efficacious effect has been demonstrated against disease caused by an HPV type already present at the time of vaccination.

Methods: We summarize data from the randomized, placebo-controlled, double-blind, international FUTURE I (NCT00092521), II (NCT00092534), and III (NCT00090220) studies that were part of the qHPV vaccine clinical program. FUTURE I and II enrolled females aged 16-26 years (N=17,622), and FUTURE III enrolled females aged 24-45 years (N=3819). HPV DNA positivity was a surrogate for current infection; anti-HPV seropositivity and HPV DNA negativity was a surrogate for past infection.

Results: Data from clinical trials showed that infection with all HPV types that are included within an HPV vaccine is notably rare. For example, infection with all four vaccine types present in the qHPV vaccine was observed in 0.1% of 3578 North American females by serology and/or HPV DNA, and none were found to be infected with all nine HPV types found in the 9-valent HPV (9vHPV) vaccine. Moreover, most prevalent HPV infections in females aged 16-25 years consist of only one or two high-risk HPV types.1 Additional analyses have demonstrated that the qHPV vaccine provides protection against HPV-related disease in females who have been exposed to HPV. In females from the FUTURE I and II trials who were infected with 1-3 vaccine HPV types, the qHPV vaccine protected against HPV-related cervical and external genital disease caused by the remaining HPV types.2 The qHPV vaccine also prevented cervical and external genital disease in females aged 16-26 years and persistent infection in females 27-45 years regardless of previous exposure to HPV vaccine types.3,4

Conclusions: HPV vaccination can protect against HPV infection and disease in unvaccinated adults who have previously been infected with vaccine HPV types; therefore, HPV vaccination should not be withheld from sexually active individuals that have been exposed to HPV.

References: 1. Barr E et al. Am J Obstet Gynecol 2008; 198: 261.e261-261.e211. 2. FUTURE II Study Group. J Infect Dis 2007; 196: 1438-1446. 3. Olsson SE et al. Human Vaccines 2009; 5: 696-704. 4. Castellsague X et al. Br J Cancer 2011; 105: 28-37.

#0523

32 - Sexually transmitted diseases and HIV infection

New sexual partnerships among sexually active US adults

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Background/Objectives: Acquisition of a new sexual partner is a risk factor for human papillomavirus (HPV) infection which can cause cervical, head and neck, anal, penile, vulvar and vaginal cancers. However, data are not available on new sexual partnerships (number, age, and sex of partners), especially among mid-adults (age 27-45 years) in the United States (US). Such data are essential for assessing exposure to HPV infection to accurately populate dynamic transmission models of sexually transmitted infections. The objective of this study was to quantify new sexual partners among sexually active US adults.

Methods: A cross-sectional online survey was conducted in 2019 with a representative sample of US adults. Respondents were from a general population online panel maintained by Lightspeed Health. Inclusion criteria were being age 18-60 years old and having been sexually active previously. We selected a random sample from the panel, with roughly equal numbers of men and women and for each 5-year age cohort. We assessed proportions with new partners, and median numbers of lifetime and new sexual partners. We also assessed the proportion of partnerships with younger (29 years) ages for age-group 25-29 years; subsequent analysis will include all age groups. We report unweighted frequencies, medians and percentages. The Pearl IRB approved this study (#19-KANT-191).

Results: Overall, 2,036 sexually active adults took the survey (1,042 women and 994 men). About half (51.8%) of the respondents were married. Median number of lifetime sexual partners was 3 vs 3, 5 vs 4, 5 vs 5, and 6.5 vs 8 for 20-24, 25-29, 30-39, and 40-44 year-old women vs. men, respectively. Having a new partner in the previous year was reported by 53.8%, 48.5%, 45.7%, 38.5%, and 29.2% of 20-24, 25-29, 30-34, 35-39, and 40-44 year-olds, respectively. Among those who acquired new partners, median number of new partners was 1 for ages 20-34, and 40-44 year-olds, and 2 for 35-39 year-olds. A total of 260 25-29 year-olds reported 358 new relationships, of which 25.2%, 52.4%, and 22.1% of the relationships were with younger, similar, and older age groups, respectively.

Conclusions: Number of lifetime partners increased across the lifespan, and many people age 20-44 years had new sexual partners in the previous year. Individuals aged 25-29 years with new partners demonstrated considerable mixing with adults in younger and older age-groups. Overall, mid-adults continue to remain sexually active and acquire new partners, although at a lower rate compared with 20-24 year-olds. Mid-adults are therefore likely to continue to be exposed to HPV infection through mid-adulthood.

#0766

2 - Epidemiology and natural history

FACTORS ASSOCIATED WITH HPV SEROPOSITIVITY IN SEXUALLY ACTIVE MEN

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Background/Objectives: Seroprevalence is a measure of cumulative HPV exposure in a population. Few studies have evaluated type-specific HPV seroprevalence in men. We assessed factors associated with seropositivity among sexually active HIV-negative men who have sex with men (MSM) and heterosexual men (HM).

Methods: In a subset of men (ages 16-26 years) participating in a global clinical trial of the quadrivalent HPV vaccine, a competitive luminex immunoassay was used to measure baseline seropositivity for HPV types targeted by the 9-valent (9v) HPV vaccine (6/11/16/18/31/33/45/52/58). Scrotal, perineal/perianal, and penile specimens were collected at baseline from all subjects and intra-anal specimens from MSM only. All were analyzed for 14 HPV types, including all 9v HPV vaccine types. Logistic regression was used to assess factors associated with seropositivity.

Results: Overall, 17% of men (683/4065; all regions) were HPV DNA-positive for at least one 9v HPV type at baseline (HM=455/3463, MSM=228/602). Among HPV DNA-positive HM and MSM, 13% (61/455) and 41% (93/228) were seropositive for a concordant type, respectively. 11% (35/333) of HM from Europe were seropositive for at least one 9v vaccine type, compared with 34% (114/335) of MSM from North America/Europe, irrespective of HPV infection status at baseline. Among MSM, factors associated with significant elevated risk of seropositivity (any 9v HPV type) at baseline included smoking (current vs never; odds ratio [OR]=1.95, 95%CI=1.20-3.18), younger age at sexual debut (<15 vs ≥20 years; OR=3.07, 95%CI=1.11-8.48) and higher number of receptive anal intercourse lifetime partners (3-6 vs 0; OR=3.61, 95%CI=1.39-9.37), whereas younger age at enrollment (16-20 vs 21-26 years; OR=0.58, 95%CI=0.34-0.98) and circumcision (OR=0.45, 95%CI=0.28-0.72) were associated with significant lower risk. No risk factors assessed were statistically significantly associated with seropositivity in HM.

Conclusions: Compared with HM, MSM had increased evidence of past HPV exposure or seroconversion. Factors associated with seropositivity in MSM only were age, smoking, sexual history, and circumcision. Most men were seronegative for all 9v HPV types, emphasizing the benefit of vaccination beyond sexual debut.

#0502

2 - Epidemiology and natural history

PREVALENCE, INCIDENCE, AND NATURAL HISTORY OF HPV INFECTION IN WOMEN AGES 24-45 PARTICIPATING IN A VACCINE TRIAL

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Background/Objectives: The natural history of HPV anogenital infection in young women has been studied extensively, but less is known about HPV natural history in mid-adult women.

Methods: We conducted secondary analyses of data from 3817 women aged 24 to 45 years who participated in a global clinical trial of the quadrivalent (4v) HPV (6/11/16/18) vaccine. Among all participants (vaccine and placebo groups), we calculated the country-specific baseline prevalence of anogenital infections for 14 HPV types: the 9-valent (9v) HPV vaccine types (6/11/16/18/31/33/45/52/58), and 5 non-vaccine high-risk types (35/39/51/56/59). Rates of incident and incident persistent infection among 989 placebo recipients naive to all 14 HPV types at baseline were estimated. Kaplan-Meier methods were utilized to estimate cumulative incidence of infection over 48 months. Cox proportional hazard models were used to estimate the risk of incident infection associated with selected baseline characteristics, including sexual behavior.

Results: Prevalence of anogenital HPV infection among women aged 24-45 varied by country and was highest in France at 29.2% (9vHPV types) and 21.7% (non-vaccine types), and lowest in the Philippines at 7.6% (9vHPV types) and 5.1% (non-vaccine types). Among the placebo recipients, HPV incidence per 100 person-years was 5.2 (9vHPV types) and 4.7 (non-vaccine types), and incidence of a persistent infection was 2.7 (9vHPV types) and 2.1 (non-vaccine types). Factors independently associated with acquiring a new infection with at least 1 high-risk HPV type targeted by the 9v vaccine included younger age, being single, current use of tobacco, younger age at sexual debut, and greater number of lifetime sex partners or new sex partners in the last 6 months.

Conclusions: Even as the incidence of new HPV infections decreases with increasing age, mid-adult women still acquire new infections, including those that persist. These findings can inform cervical cancer screening programs and HPV vaccination strategies targeting adult women who were not vaccinated as adolescents.

#0731

5 - HPV prophylactic vaccines

NATURAL PROGRESSION OF PERSISTENT HPV INFECTION AND THE RESULTING BURDEN OF HPV-RELATED DISEASE IN ADULT WOMEN

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Background/Objectives: Placebo and active control recipients from the quadrivalent human papillomavirus (qHPV) and nine-valent HPV (9vHPV) vaccine clinical trial programs are a potential source of robust data that are not typically available from observational studies. These participants have not been protected from infection by all or some of the 9vHPV vaccine types (HPV 6/11/16/18/31/33/45/52/58) and received follow-up every ~6 months; therefore, evidence of the progression from persistent HPV infection to cervical intraepithelial neoplasia grade 2+ (CIN2+) could be obtained. We summarize data from three prospective qHPV and 9vHPV vaccine trials in women aged 16-45 years to assess the natural progression of 9vHPV vaccine-related persistent infections.

Methods: Data were included from the placebo arms of two qHPV vaccine trials in women aged 16-23 years (NCT00092482; n=1,788) and aged 27-45 years (NCT00090220; n=1,629). In addition, data were included from an active qHPV vaccine control arm from a 9vHPV vaccine trial; participants were aged 16-26 years (NCT00543543; n=7,105). All evaluable participants (n=10,522) were assessed for the baseline prevalence of 9vHPV vaccine type infections using polymerase chain reaction and serological testing. Using data from regular follow-up visits, the median time to clearance of persistent infection (of ≥6 month's duration) with HPV 16/18/31/33/45/52/58 was determined, and the proportion of persistent infections that progressed to CIN2+ was assessed. All findings were summarized by age group and HPV type.

Results: Baseline data from the three trials showed that among women aged 27-45 years, 18% were positive to ≥1 of the 9vHPV vaccine types and 0% were positive to all 9vHPV vaccine types. The percentage of participants who cleared persistent HPV infections and the percentage of persistent HPV infections that progressed to CIN2+ was fairly similar across age groups and HPV types. Across the 9vHPV vaccine types in women aged 16-45 years, and across age groups, the median duration for the clearance of persistent infections was between 1.0-1.5 years, and the median time to progression of persistent infections to CIN2+ was between 0.3-1.4 years.

Conclusions: Based on epidemiological data in US women aged ≥30 years, approximately 97,000 annual cases of CIN2+ were attributable to HPV types 6/11/16/18/31/33/45/52/58 in 2016, [1] representing a substantial burden of HPV-related disease in women aged >26 years. Given that in our study the median duration from persistent infection to CIN2+ was ≤1.5 years, most CIN2+ cases in women aged ≥30 years will have likely resulted from infections acquired after the age of 26 years.

References: 1. McClung, N.M., et al., Estimated Number of Cases of High-Grade Cervical Lesions Diagnosed Among Women - United States, 2008 and 2016. MMWR Morb Mortal Wkly Rep, 2019. 68(15): p. 337-343.

#0521

2 - Epidemiology and natural history

Median age at onset of cervical HPV infection and diagnoses of cervical pre-cancers among women in the United States

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Background/Objectives: Human papillomavirus (HPV) is the most common sexually-transmitted infection globally and is the cause of cervical cancer with 11,788 new HPV-associated cases in the U.S. in 2015). HPV infection is asymptomatic, but HPV-related precancers such as cervical intraepithelial neoplasia 2+ (CIN2+) can be diagnosed through cervical screening. A model-based study estimated the median age of causal HPV infection at 20.6 years. This study utilized a new approach and estimated median age at causal HPV infection using real world data on incidence of CIN2+ and screening, prior to widespread use of HPV vaccination.

Methods: We estimated the age of causal HPV infection as follows: (age of CIN2+ diagnosis) - (time from CIN2+ onset to CIN2+ diagnosis) - (time of progression from HPV infection to CIN2+ onset). Age at CIN2+ diagnosis was obtained through analysis of data on age-specific diagnosis of CIN2+, sourced from Connecticut CIN2+ surveillance registry from 2008-09. Time from CIN2+ onset to CIN2+ diagnosis was assumed to be the time taken to screen half of the population, based on Connecticut data from 2008 Behavioral Risk Factor Surveillance System (BRFSS) survey on the proportion of women screened in the previous 3 years. Time from HPV infection to CIN2+ onset was estimated from peer-reviewed clinical trial-based publications. We estimated median (vs mean) as it provides a more accurate estimate of when 50% of the population can still be protected through vaccination, and it is lower vs. mean. A discrete event simulation is underway to report detailed statistics.

Results: A total of 6,083 cases of CIN2+ were reported in Connecticut in 2008-09, with median age at CIN2+ diagnosis of 28 years. The median time from CIN2+ onset to diagnosis was estimated to be 1.5-2 years based on 91% and 69% of women age 25-54 and 18-24 years, respectively, who reported having had a Pap test in the past 3 years. The estimated median time from HPV infection to CIN2+ onset from literature review was 1.5 years. Taken together, these findings inferred that HPV acquisition is likely to precede CIN2+ diagnosis by 3-3.5 years. The median age at causal HPV acquisition was estimated at 24.5-25 years.

Conclusions: We estimate that half of causal HPV infections in women occur after 24.0-25.5 years of age. As individuals are likely to continue to acquire causal HPV infections as mid-adults, HPV vaccination of mid-adults could provide public health and economic value. Since CIN2+ diagnoses are based on screening modalities, research on understanding the natural history of HPV infection and cervical screening is needed to better ascertain the median age at HPV infection.

#0446

5 - HPV prophylactic vaccines

9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE EFFICACY IN WOMEN WITH PRIOR HPV EXPOSURE: COMPARISON WITH HISTORIC PLACEBO POPULATION

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Background/Objectives: The 9vHPV vaccine protects against diseases resulting from infection by the 4 HPV types contained in the quadrivalent vaccine (qHPV; HPV6/11/16/18) and five additional oncogenic types (HPV31/33/45/52/58). We report efficacy estimates against cervical, vulvar, and vaginal disease caused by all 9 vaccine HPV types and prevention of related cervical surgeries compared with a historic placebo population.

Methods: Three international, randomized, double-blind studies were conducted in women aged 16-26 years; the pivotal efficacy study evaluating the 9vHPV vaccine (n=7106) vs. qHPV vaccine (n=7109) (NCT00543543) and historic efficacy studies of qHPV vaccine (n=8810) vs. placebo (n=8812) (FUTURE I [NCT00092521] and FUTURE II [NCT00092534]). End-of-study data were used to evaluate 9vHPV vaccine efficacy and incidence rates compared with placebo by baseline vaccine HPV type status (assessed by PCR) in a modified intent-to-treat population.

Results: Among women who were negative for all 9vHPV vaccine types, cervical disease of any grade and high grade related to HPV 6, 11, 16 or 18 was significantly reduced compared with placebo by 99.0% and 100%, respectively, and HPV31/33/45/52/58-related disease was reduced by 96.9% and 95.3%, respectively. The 9vHPV vaccine did not prevent disease related to vaccine HPV types detected at baseline but significantly reduced cervical, vulvar, and vaginal diseases related to other vaccine HPV types. HPV31/33/45/52/58-related cervical disease was reduced among women who were positive for HPV6, 11, 16, or 18 but negative for HPV31, 33, 45, 52, and 58 at baseline (any grade, 95.1%; high grade, 91.1%). Similarly, HPV6/11/16/18-related cervical disease incidence was significantly reduced vs. placebo among women who were HPV6, 11, 16 and 18-negative at baseline but positive for HPV31, 33, 45, 52 or 58 (any grade, 97.4%; high grade, 95.8%). Reductions in the incidence of biopsy and definitive therapy of ≥93.0% were observed for HPV6/11/16/18-related and HPV31/33/45/52/58-related lesions among women who were negative for the respective HPV types at baseline, including those who were positive for other 9vHPV vaccine types.

Conclusions: The 9vHPV vaccine reduces cervical, vulvar and vaginal disease caused by the targeted HPV types compared with a population of unvaccinated women. Among women positive for one or more HPV types at trial enrollment, efficacy against other targeted HPV types was maintained. These data support the potential for the 9vHPV vaccine to prevent disease among sexually active, HPV-infected women.

References: Giuliano AR et al. Gynecol Oncol. 2019; 154; 110-117.

#0796

5 - HPV prophylactic vaccines

Public health and economic benefit of expanding HPV vaccination to mid-adult populations

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Background/Objectives: In Oct. 2018, the US FDA approved the use of the nonavalent human papillomavirus vaccine in the 27-45 year-old age group. Subsequently, the Advisory Committee on Immunization Practices updated the recommended routine vaccination at age 11-12 years, catch-up vaccination until age 26 years, and shared clinical decision-making for ages 27-45 year old (expanded recommendation), from the previous recommendation in which routine vaccination was recommended for age 11-12 years, catch-up vaccination was recommended for females through age 26 years and males only through age 21 years; older adults were not recommended (status quo). This study assesses the public health and economic impact of expanded vaccination compared with status quo in the US.

Methods: A published and validated non-linear, deterministic, model of the transmission dynamics of HPV infection and disease was updated and used to estimate disease outcomes, pre-vaccination median age at (acquisition of) HPV infection, quality-adjusted life years (QALY), costs, and incremental cost-effectiveness ratio (ICER) of expanded vaccination compared with status quo. We estimated historical vaccination coverage (HVC) using NIS-TEEN survey data from 2007-2016. Costs were estimated from a payer perspective (2018 USD). We assume annual uptake of 3.5% and 2.8% for adult females and males. We adopted a 100-year time horizon (2019 to 2119), and discounted (costs/benefits) at 3% per annum. Scenario analyses conducted included restricting upper age limit to 27, 30, and 35 years and limiting catch-up to 10 years. Sensitivity analysis included using NHANES survey data for HVC.

Results: The modeled pre-vaccination median age at HPV infection was estimated to be 27-30 years old. Expanded vaccination would prevent 37,856 HPV-related cancers, 171,472 CIN1 cases, 314,468 CIN2/3 cases 1,743,461 genital wart cases, and 10,698 deaths compared with status quo over 100 years, with an ICER of $141,000/QALY. The ICERs for restricting the upper age limit to 35 years, and 10-year catch-up were $107,000/QALY, and $116,000 /QALY, respectively. The ICER using NHANES data for HVC was $82,000/QALY.

Conclusions: The economic value of the vaccine is sensitive to the underlying assumption regarding HVC, the upper age limit of the expanded vaccination program, and the duration of the catch-up program and could be considered cost-effective in some scenarios. Given the high estimated median age of HPV infection, a substantial burden of HPV among 27-45 year-olds can be averted through expanded vaccination of 9-45 year-olds in the US.

HN 04B - HPV and oropharynx / Head and Neck cancer (submitted papers)

#0084

29 - HPV and oropharynx / Head and neck cancer

GENETIC HETEROGENEITY IN OPSCC REVEALED BY SINGLE-CELL RNA SEQUENCING

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Background/Objectives: Oropharyngeal squamous cell carcinoma (OPSCC) is a heterogenous tumour type due to the high mutation rate in HPV- and the process of viral integration in HPV+ tumours. This heterogeneity contributes to drug resistance and tumour progression. Single-cell RNA sequencing (scRNASeq) allows analysis of tumours with an unprecedented resolution, enabling identification of small but biologically significant populations of cancer and stromal cells that have an impact on prognosis and drug sensitivity. Our aim was to prove the feasibility of large-scale scRNASeq in OPSCC through characterising these subpopulations and their functions in a large number of patients with the end goal of improved patient stratification to avoid overtreatment as well as identifying new treatment targets.

Methods: 16 patients with OPSCC, 3 HPV- and 13 HPV16+, undergoing curative surgery 2018-19 were included in the study. Fresh tumour samples were dissociated into a single-cell suspension. Cells were barcoded using the Chromium 10x system, followed by Illumina sequencing. The generated sequences were aligned to the human transcriptome as well as the transcriptomes of HPV 16, 18, 31, 33 and 35. Cells were clustered and their gene expression patterns examined to define the major cell types. Cancer cells were defined by the presence of copy number aberrations (CNA) inferred through mRNA expression across chromosomal regions. Gene expression patterns recurring in cell populations from multiple patients were combined into metaprograms representing biological functions.

Results: More than 60000 cells were identified and could be classified to cell type by their gene expression. In cancer cells, metaprograms representing senescence, proliferation, epithelial-mesenchymal transition and stemness were found. Clonal tumour evolution could be traced through identifying cells with differing CNA in the same tumour. Particularly interesting were the findings that one p16+ tumour could be reclassified as HPV- due to absence of HPV transcripts, while another tumour showed two highly distinct CNA patterns, suggesting two biologically unrelated tumours in the same location.

Conclusions: This is, to date, the largest single-cell transcriptomic study of head and neck cancer. We provide a comprehensive map of the tumour ecosystem and identify distinct subpopulations of biological significance in all the major cell types that make up the tumour. Our re-classification of a p16-positive tumour, clonal evolution tracing and identification of cancer cell populations with different biological functions highlight the potential for single-cell technology to be used in pathology for improved patient stratification and treatment selection.

#0315

29 - HPV and oropharynx / Head and neck cancer

IMPROVED DETECTION OF PROMISING EPIGENETIC BIOMARKERS FOR HEAD AND NECK CANCER IN SALIVA

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Background/Objectives: Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease, encompassing malignancies arising in the hypopharynx, oropharynx, the nasal and oral cavities, and larynx. Two thirds of patients are diagnosed with advanced tumour stages, mainly after the onset of symptoms. This results in an overall 5-year survival rate of less than 50 %. Therefore, non-invasive diagnostic tools for early and precise detection need to be established. For this purpose, we currently conduct the feasibility study OncSaliva, with the aim to prove that cancer-specific epigenetic markers, detected in DNA from primary tumour tissue, may also be detectable in non-invasive saliva samples and blood.

Methods: Before starting the OncSaliva study, we validated the methylation-specific multiplex PCR assay based on the detection of HNSCC-specific DNA methylation markers (Z1-Z5; reference ACTB), using fresh-frozen tissue samples (20x HNSCC; 20x controls). The aim is to include 200 patients in the OncSaliva study. For multiplex QPCR testing fresh frozen tissue, saliva and cfDNA from blood are collected from each HNSCC patient at the Department of Otorhinolaryngology, Jena University Hospital. Isolated genomic DNA was bisulfite-converted before use in multiplex QPCR assay using the cobas z 480 analyzer (Roche). Calculations of the clinical sensitivity and specificity as well as methylation level in relation to the reference were used for performance evaluation of the assay.

Results: Validation of the five head and neck cancer-specific methylation markers (Z1 - Z5) by multiplex QPCR yielded 100 % clinical sensitivity and 95 % specificity, if at least one out of five markers was positive in HNSCC (n=40). Single marker results ranged from 30 % to 70 % sensitivity and 95 % to 100 % specificity in this validation sample set. First data from the OncSaliva study with tissue, saliva and blood from six HNSCC patients revealed a positive detection of the markers Z1, Z3-Z5 in all tissue samples. Furthermore, positive detection of Z1 was concordant between all six tissue and the respective saliva samples, but for only two cfDNA samples. Marker Z5 showed positive detection in 6/6 tissue and 5/6 saliva samples. Marker Z2 - Z4 had weak detection rates in saliva samples so far. Results of the control group are not yet available.

Conclusions: Preliminary results from validation and recent patient samples support our study hypothesis which envisages a robust detection of HNSCC markers in both, tissue and saliva. Utilization of saliva samples for local and easy-to-use sample collection for application in a cancer-specific multiplex assay will be useful as an in vitro diagnostic strategy in secondary and tertiary prevention.

#0642

29 - HPV and oropharynx / Head and neck cancer

FGFR3 mutations are less common in HPV- TSCC/BOTSCC

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Background/Objectives: Human papillomavirus positive (HPV+) tonsillar and base of tongue squamous cell carcinoma (TSCC/BOTSCC) have better outcome than corresponding HPV-negative (HPV-) cancers. The Global Cancer Observatory/WHO rates in Romania with 7,8 for males the estimated age-standardized incidence rates (World) in 2018, for oropharynx, being one of the highest in Europe. With this pilot study we aimed to analyse potential risk factors in Romanian TSCC/BOTSCC selected patients.

Methods: 20 TSCC/BOTSCC cases (from Iasi, Romania) were tested for HPV and for FGFR3 protein expression. The study was performed according to permission 2009/1278- 31/4 from the Ethical Committee at Karolinska Institutet and permission 3953 (2018) from the University of Medicine and Pharmacy, Grigore T Popa, Iasi, Romania.HPV DNA status was assayed by a PCR-based bead-based multiplex-assay on a MagPix instrument (Luminex Inc.). Detection of FGFR3 mutations was performed by Competitive Allele-Specific Taqman® PCR technology (Thermo Fischer Scientific, Waltham, MA, USA). The analysis was performed in 384-well plates, in 10 µl comprising 5 µl 2X Taqman Genotyping Mastermix (Thermo Fischer Scientific, Waltham, MA, USA), 0.2 µl 50X Exogenous IPC template DNA, 1 µl 10X Exogenous IPC mix, 1 µl Mutation Detection Assay, 1.8 µl deionized water and 20 ng DNA (in 1 µl). Runs were performed on an Applied Biosystems 7900HT Fast Real-Time PCR System using the following set of reaction conditions: 95ËšC, 10 min followed by 5 cycles at 92ËšC, 15 sec and 58ËšC, 1 min and 40 cycles at 92ËšC for 15 sec and 60ËšC for 1 min. The Mutation Detection Assays were Hs00000811_mu, Hs00000812_mu, Hs00001342_mu, which detects variants p.R248C, p.S249C and p.K650Q in FGFR3 gene respectively, and reference assay Hs00001015_rf was used for detection of wild-type FGFR3.

Results: All the tested samples were HPV- and all these exhibited wild-type FGFR3.

Conclusions: For the selected patients we found no HPV positive samples, indicating that maybe there are involved some other risk factors (e.g., smoking). This finding was in concordance with the previous sequencing data showing a very low frequency of mutated FGFR3 (1/46, 2.1%) among HPV- samples and we have confirmed by this that FGFR3 mutations were less common in HPV- TSCC/BOTSCC.

References: Bersani C, Haeggblom L, Ursu RG, Giusca SE, Marklund L, Ramqvist T, Näsman A, Dalianis T., Overexpression of FGFR3 in HPV-positive Tonsillar and Base of Tongue Cancer Is Correlated to Outcome., Anticancer Res. 2018 Aug;38(8):4683-4690. doi: 10.21873/anticanres.12774. Acknowledgements: RGU is supported by the University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania (grant no. 30336 / 28.12.2017).

#0668

29 - HPV and oropharynx / Head and neck cancer

Antitumor effects in vitro of FGFR and PI3K inhibitors on human papillomavirus positive and negative tonsillar and base of tongue cancer.

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Background/Objectives: To examine if targeted therapy is an option for tonsillar and base of tongue squamous cell carcinoma, two human papillomavirus positive (HPV+) and one HPV-negative (HPV-) tonsillar and base of tongue squamous cell carcinoma cell lines were tested for their sensitivity towards FGFR and PI3K inhibitors. Human papillomavirus positive (HPV+) tonsillar and base of tongue squamous cell carcinoma have better outcome than corresponding HPV-negative (HPV-) cancers. However, not all patients with tonsillar and base of tongue squamous cell carcinoma do well and additional therapies would be of use. Recently, we demonstrated that FGFR3 and PIK3CA are often mutated in HPV+ cancer. Furthermore, there are FGFR and PI3K targeted therapies that are used for other types of cancer e.g. bladder cancer. For this

Methods: HPV+ UM-SCC-47 and UPCI-SCC-154, and HPV- UT-SSC-60A were tested by competitive allele-specific TaqMan-PCR (CAST-PCR) for presence/absence of frequently occurring FGFR3 and PIK3CA mutations. All cells were then treated with FGFR inhibitor AZD4547 and PI3K inhibitors BEZ235 and BKM120 alone, or with AZD4547 and BEZ235 in combination. Viability was analyzed by a WST-1 assay, cytotoxicity tested by a CellTox Green cytotoxicity assay, apoptosis analyzed by a Caspase Glo 3/7 assay, and proliferation examined with the xCELLigence System.

Results: HPV+ UM-SCC-47 and UPCI-SCC-154, and HPV- UT-SSC-60A, did not exhibit any common FGFR3 or PIK3CA mutations, but were all sensitive to FGFR inhibitor AZD4547 and PI3K inhibitors BEZ235 and BKM120. Notably, HPV+ UPCI-SCC-154 was generally slightly more sensitive than the other two cell lines. Furthermore, when AZD4547 and BEZ235 treatment was combined in HPV+ UPCI-SCC-154 and HPV- UT-SSC-60A, potentiated combination effects were observed.

Conclusions: HPV+ UM-SCC-47 and UPCI-SCC-154, and HPV- UT-SSC-60A had no common FGFR3 or PIK3CA mutations, but were sensitive to FGFR inhibitor AZD4547, and PI3K inhibitors BEZ235 and BKM120. Furthermore, the latter two cell lines were, especially sensitive to combinations of AZD4547 and BEZ235.

#0148

7 - Immunotherapy - Immuno-oncology - New treatments

VACCINIA VIRUS AS TOOLS FOR THE TREATMENT OF HPV LESIONS IN LARYNX

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Background/Objectives: Background:Recurrent respiratory papillomatosis (RRP) or laryngeal papillomatosis is a disease caused by papillomavirus infection.

Methods: Methods:In this phase I/II clinical trial, we evaluated theefficacy of themodified vaccinia Ankara (MVA) E2 virus in the treatment of RRP.Twenty-nine patients(18 female and 11 male)underwent injection ofMVA E2 directly into the borders of the vocal cords where lesions were present, andweremonitored by directlaryngoscopy.The immune response wasassessed bydetermination of CD3+, CD4+, and CD8+lymphocytescounts. The presence of papillomavirus was determined by PCRanalysis.

Results: Results:Lesions were completely eliminated in 13patients(44.8 %). In 16patients(55.2 %),lesions recurred between 6 and 18 months after treatment;these patients received a second round of treatment with MVA E2, and they have not presented with new recurrences.

Conclusions: Conclusion:The MVA E2 vaccine has excellent potential for generating complete regression of RRP lesions.

References: References [Beltran, Oand Rosales R. (2018).Therapeutic Vaccinemarkedly reduces the likelihood of recurrence of respiratory papillomatosis. Head & Neck; 1-9] [Rosales, R., Lopez-Contreras, M., et al, and Villarreal, F. (2014). Regression of Human Papillomavirus Intraepithelial Lesions is induced by MVA E2 therapeutic vaccine. Human Gene Therapy. 25 (12): 1035-1049.] [Albarran y Carvajal, A., de la Garza, A., et al,and Rosales R.(2006). A Phase I/II Study: MVA E2 Recombinant Vaccine in the treatment of papillomavirus infection in men presenting intraurethral flat condyloma. Bio Drugs.20 (6): 1] [García-Hernández, E., González-Sánchez, JL., et al, and Rosales R(2006). Regression of papilloma high-grade lesions (CIN 2 and CIN 3) is stimulated by therapeutic vaccination with MVA E2 recombinant vaccine. Cancer Gene Therapy. 13 (6): 592-597] [Carlos Manuel Corona Gutierrez, Alberto Tinoco, et al and Ricardo Rosales(2004). Therapeutic Vaccination with MVA E2 is able to Eliminate Precancerous Lesions (CIN I, CIN II and CIN III) Associated with Infection of Oncogenic Human Papillomavirus. Human Gene Therapy. 15(5): 421-431.] [Rosales, C., Valadez-Graham V., et al and Rosales R. (2000). MVA E2 a Recombinant Vaccinia Containing the papilloma Virus E2 Protein Promotes Tumor Regression by Stimulating Macrophage Antibody-Dependent Cytotoxicity. Cancer Immunology Immunotherapy. 49 (7):347-360.] [Valadez, G. V., Sutter, Get al and Rosales, R. (2000). The highly attenuated MVA strain of vaccinia virus carrying the E2 gene of bovine papillomavirus is able to stop growth of human tumors generated in nude mice. Cancer 88 (7): 1650-1662.]

#0496

29 - HPV and oropharynx / Head and neck cancer

ROLE OF HYPOXIA'S FACTORS IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA (OPSCC): A DIGITAL APPROACH.

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Background/Objectives: In the last decades we withnessed a rapid expansion of OPSCC cases related to oncogenic high-risk HPV infection, whose spreading in some regions has been referred to as epidemic 1. HPV-negative (HPV-) and HPV-positive (HPV+) OPSCC tumors represent two different clinicopathological and molecular entities, HPV+ OPSCCs generally showing better survival than HPV unrelated cancers. However, HPV positivity assessment alone, determined by p16 IHC, according to last TNM classification 2, is not able to predict the real clinical behavior for all OPSCC cases. Proteins involved in response to hypoxic stress are increasingly used to predict the aggressiveness of malignant tumors. Carbonic anhydrase IX (CAIX) is a protein induced by hypoxia, with different roles in the development of cancer and/or chemo-radio resistance and could represent a therapeutic target for solid tumors 3-5. The immunohistochemical overexpression of CAIX in HNSCC has been recently reported. However, the assessment of tumor cells' positivity is quite heterogeneous since there is huge variability in cut-off values, with percentages ranging from 1% to 50% of neoplastic cells positivity, and with the application of either qualitative or semi-quantitative scales; slides are mostly evaluated by pathologists without the support of quantitative analysis, or combining variously quantitative and qualitative assessment 6-7.

Methods: We evaluated the expression of the CAIX protein on tissue microarray section (TMA) obtained from FFPE OPSCC tissues, using digital image analysis (DIA) and QuPath 8, an open-source software. We established an automatic image processing approach to reliably quantify non-tumor and tumor-cells, and, in this group, separating positive and negative tumor cells by means of CAIX immunohistochemical expression. Two expert pathologists confirmed the reliability of the process. We used the X-Tile software 9 to identify the best cut-off for CAIX expression.

Results: In our study population, CAIX was overexpressed in OPSCC with a poor outcome (Log Rank test $p<0.01$), as assessed by Kaplan-Meier curves. Through a box-plot diagram, we evidenced that HPV+ cases were characterized by lower expression levels of CAIX compared to HPV- ones, confirming the observation that HPV-positive OPSCCs are less hypoxic than their negative counterpart 10.

Conclusions: According to these results, it seems possible to stratify the risk of OPSCC tumors basing on the CAIX protein levels. The DIA approach was found to be an accurate method to reduce the number of equivocal cases, especially on TMAs.

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OPENING CEREMONY

#1041

1 - Viral and molecular biology

FORTY YEARS OF HPV AND CANCER

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Background/Objectives: The study of the role of Human Papillomavirus in cervical cancer and then in other cancers has produced a sea-change in the approach to the prevention of cervical and other HPV-related cancers in the forty years since Harald zur Hausen and his laboratory in Heidelberg found HPV in cervical cancers and characterised HPV16. He was awarded the Nobel prize for his contribution, but continuing research into HPV extended from his work and that of a few other enthusiasts in the early 1980's and before to involve thousands of researchers of many different disciplines and many others increasingly over the last 40 years. The historical review book project was started in 2016 and has involved 58 researchers of different backgrounds and seniorities to set down in Scientific American style their account of how all the evidence accumulated on the role of HPV in cancer and its prevention from the early stages up to current research and preventive practice, and produce an accessible review of the current state of knowledge. It covers the many very different disciplines from molecular virology, through clinical and epidemiological research including the huge trials of HPV screening and of vaccines, health economic modelling and psychosocial study of the problems of HPV vaccination and the anti-vaxx issues. The present talk summarise the important stages of development of knowledge from before HPV was recognised and cervical cancer prevention did not exist. It begins with the first descriptions in the Greco-Roman world of what would now be recognised as cervical cancer: an extremely unpleasant, embarrassing and nasty fatal disease of young women, certainly not confined to the poor or promiscuous in the Western population and traces the important stages of developing evidence about HPV through research. HPV science has been an amazing example of the success of modern technological, evidence-based medicine and the importance of international collaboration between academics, industry and regulatory and governmental bodies in achieving this end. The development of HPV science and its impact on medical practice is very much a modern example of the Pasteurian dictum - "Fortune favours the prepared mind". Given a major key into cervical and a few other cancers the system of international medical science has worked well, and expertise and new technology has permitted huge expansion, despite initial scepticism in some quarters. However, the spread of effective prevention to eliminate cervical cancer throughout the whole world, as proposed by the WHO depends on convincing politicians, other funders and the people of many countries of the importance and safety of preventing cervical cancer and other HPV related disease.

Methods: xxx

Results: xxx

Conclusions: xxx

SS 04 - Wider use of HPV self-sampling in screening programs: current practice

#0255

10 - Self-sampling

THE NETHERLANDS : DATA FROM THE FIRST COUNTRY OFFERING WOMEN THE POSSIBILITY TO SELF-COLLECT SAMPLES FOR HPV TESTING

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Background/Objectives: ln 2017 population-based screening for cervical cancer in the Netherlands has been changed from primary morphological to primary hrHPV screening. Despite the highly organized program, only about 65% of the women participate in the screening. As self-collected samples are as sensitive for hrHPV testing as GP-collected samples, incorporating self-collected samples in the screening may overcome the issues of non-responding women and increase the participation rate. Therefore, from the start of the new hrHPV-based screening in 2017, ALL women are offered the possibility for self-collecting their own sample.

Methods: On request (opt-in) an Evalyn brush for self-sampling is sent to the women, and after collecting the self-sample is directly send to the screening laboratory. If a woman is hrHPV positive in her self-sample, she is requested to visit her GP for an additional cervical scrape for cytomorphological screening as the self-sample is not reliable for cytology. Although not actively promoted, a trend to increased numbers of self-collection is observed since the beginning of the hrHPV screening.

Results: In 2018 (reference date March 2019), 799,257 invitations were send and 460,855 women actually participated (58%), which is still slightly lower than in the original program. Of the participating women, 31,075 (6.7%) requested a self-collecting device. Although younger women (30-24 years old) were more in favor for self-collecting (9.6%), the number of women requesting a self-sample in the remainder age groups is equally distributed. The number of hrHPV positive women in the self-collected sample (7.8%) is slightly lower than the number of hrHPV positive women in the GP-collected sample (9.6%). The age distribution of hrHPV positive women in the self- and GP-collected samples is the same, higher percentage in the younger women to the lowest hrHPV percentages in the older women. Importantly, the % of cervical abnormalities in the GP-collected samples and in the GP-collected samples after an hrHPV positive self-collected sample, were equal. In about 67% of the hrHPV samples (either GP or self-collected) no abnormal cells were found (Pap1), to about 4.5% of the samples having a severe dysplasia (Pap3B).

Conclusions: The primary hrHPV screening for cervical cancer is running successfully, although the number of participating women is still a bit lower than was anticipated. The hrHPV positivity in self-collected samples is lower than in GP-collected samples although the cervical abnormalities found is equal in both groups. This suggests that self-sampling has a bit lower sensitivity in detecting hrHPV but a higher specificity. These issues will be discussed during the presentation.

#0689

14 - Screening methods

MD PhD

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Background/Objectives: Cervical cancer elimination can be achieved if 90% of adolescent girls are vaccinated and 70% of women aged 35-45 years of age are screened with a high precision HPV test. In Malaysia, while the National HPV vaccination program has been a success, the cervical screening uptake at 12.8% is currently below the recommended rate by World Health Organization. The reasons commonly quoted for the poor uptake of regular Pap smears include embarrassment, discomfort, fear of pelvic examinations, lack of time, feeling they are unnecessary and not relevant to them. Project ROSE (Removing Obstacles to Cervical ScrEening) explores a solution to increase cervical screening uptake in Malaysia integrating self-sampling for HPV testing and E-mobile technology. Self-sampling (low vaginal) was undertaken using the Copan FLOQswab®. The returned FLOQswab® was sent for HPV testing under 1 week on a validated platform. The ROSE screening method was could be replicated in both community clinics and at ad-hoc community events where more than 100 women can be screened within 4 hours. The feasibility, acceptability and performance of self-sampling as a primary cervical screening tool in both communit health clinics and community events among Malaysian women will be presented.

Methods: Two different platforms were used for HPV testing- Cepheid HPV GeneXpert and ROCHE COBAS 4800. Telephone surveys were conducted among 1,000 (out of 4355) randomly selected Malaysian women between ages 30 to 65 years who had completed self-sampling using a vaginal self-swab for primary HPV testing as part of a cervical screening pilot program within five community health clinics under Project ROSE. The survey evaluated participants' acceptability towards this self-sampling method. In addition, women who attend community events are also asked to report their experience immediately after they perform the screens upon handing in the swabs.

Results: Among the 4188 self- acquired swabs in the clinic setting, only 0.48% came back with an invalid rate at first pass. In terms of acceptability, it was found that 99% of participants would be willing to perform this self-sampling method again, 97% would recommend it to family and friends, and 94% preferred the self-sampling method compared to the Pap smear that requires a pelvic examination. The main reasons cited by participants for preferring the ROSE method for cervical screening included that it was simple (98%), quick (94%) and self-performed (95%). Furthermore, 28% of participants had never done a Pap smear before and 45% were overdue for screening. In the community setting, the invalid rates varied between 2-4.5%. Reasons for this will be discussed

Conclusions: A cervical screening strategy that utilizes self-sampling was found to be feasible and highly acceptable among Malaysian women with more than 99% indicating they would be happy to perform the test again as it allows women to perform the test on their own, is more convenient, allows privacy, and takes a shorter time to complete compared to the Pap smear.

SS 06 - Cervical cancer screening and immunization in low and middle income countries

#1052

10 - Self-sampling

Use of self-sampling as a screening method in LMIC

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Background/Objectives: Despite more than 50 years of valiant efforts and huge financial outlay the control of cervical cancer remains elusive. We need every tool we can muster in the fight against this deadly but completely preventable disease. Self-collection of exfoliated cells is broadly recognized as an important new way to improve access and reduce screening costs.

Methods: Review of published studies, systematic reviews and meta-analyses.

Results: More than 30 randomized controlled trials and observational studies, including upwards of 350,000 women, have been completed with most studies done in developed countries. Investigators explored various demographic and performance aspects of vaginal or urine self-collection with HPV DNA testing. There is very strong evidence that self-sampling offers a convenient, cost-effective, highly acceptable and safe cervical screening option to women in all countries, including LMIC. The sensitivity and specificity of HPV DNA testing from self-collected samples is almost as good as from clinician-collected samples, with sensitivity and specificity for CIN3 or cancer approaching 90%, regardless of level of local economic development. There is strong evidence that providing an option of self-collection to women in rural and economically deprived regions can increase uptake of screening and greatly improve the detection of precancers, thereby offering hope for prevention of cervical malignancy.

Conclusions: HPV DNA testing of self-collected samples has been extensively proven as essentially equivalent to clinician collected samples. Screening programmes using self-collected samples are ready for routine use in LMIC and can safely replace cytology and HPV testing from clinician-collected samples.

References: Lazcano-PonceE*, Lorincz AT*, Cruz-Valdes A, Salmeron J, Uribe P, Velasco-Mondragón E, Hernandez Nevarez P, Diaz Acosta R, Hernández-Avila M. 2011. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. (*Co-first authors). Lancet 378: 1868-873.

HN 05 - Head & Neck Forum - Surveillance for recurrent HPV

#1044

29 - HPV and oropharynx / Head and neck cancer

HPV ANTIBODIES AND RISK OF RECURRENCE

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Background/Objectives: Not all patients with human papillomavirus-driven oropharyngeal cancer (HPV-OPC) have favorable outcomes. Accurate risk stratification has important implications for treatment and post-treatment surveillance. Yet, there are few clinical and no molecular markers of HPV-OPC recurrence. Several small studies have evaluated HPV16 E6 antibodies as a potential prognostic marker; however, results are conflicting. The specific details of each study as well as future directions will be discussed.

Methods: N/A

Results: N/A

Conclusions: N/A

MSS 01 - Ecology of HPV in the post vaccination era

#1037

5 - HPV prophylactic vaccines

Systematic review of analyses of HPV type-replacement following vaccination programs

Mesher D[1]

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Background/Objectives: Background / Objectives

Methods: Methods

Results: Results

Conclusions: Conclusion

#0380

2 - Epidemiology and natural history

HPV TYPE REPLACEMENT IN POPULATIONS FOLLOWING GIRLS-ONLY AND GENDER-NEUTRAL VACCINATION

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Background/Objectives: The selective pressure applied by gender-neutral or girls only HPV vaccination on a selected number of high-risk HPV types, may result in replacement of vaccine-covered types by non-vaccine HPV types. We evaluated the occurrence of HPV type replacement in a population-based follow-up of a community randomised HPV vaccination trial.

Methods: In 2007-10, 33 Finnish communities were randomised to receive gender-neutral [Arm A], girls only [Arm B] HPV vaccination, or gender-neutral Hepatitis-B vaccination [Arm C] of 1992-95 born early adolescents. 20,513, girls, and 11,662 boys were vaccinated with moderate vaccination coverage. Self-collected cervicovaginal chlamydia samples (11,396) at aged 18 were HPV typed using high throughput MALDI-TOF PCR. We retrieved 8022 biobanked serum samples from 2005-10 and 2011-16, pre- and post-vaccination eras, from unvaccinated females aged <23 at sample donation, and resident in the trial communities. Serum samples were analysed for the presence of antibodies to 17 HPV types and herpes simplex virus type II (HSV-2) using multiplexed pseudovirion Luminex assays. Vaccine and non-vaccine type HPV prevalence among the trial participants was compared as a prevalence ratio (PR) between the trial Arms, to evaluate niche clearance and type replacement occurrence respectively. Likewise, HPV seroprevalence by trial Arm was compared pre- and post-vaccination era among the unvaccinated women. All comparisons were stratified by a proxy measure of core-group membership.

Results: HPV51 prevalence was increased among the unvaccinated 1992-94 born women in the gender neutral Arm A as compared to the control Arm C (PR= 1.49 [1.01-2.19]). The HPV51 prevalence increase was greater in the unvaccinated participants among the core group, identified by C. trachomatis proxy. During the post-vaccination era, the HPV16 seroprevalence decreased among the unvaccinated women resident in the gender-neutral Arm A, whereas for HPV51 the PR was 1.04. Among the core-group of adolescents, identified by HSV-2 seropositivity proxy, the HPV51 seroprevalence increased albeit only marginally (PR=1.21 [0.53-2.78]).

Conclusions: When vaccination coverage is moderate, the degree of HPV16 niche clearance is greater under gender-neutral vaccination. HPV51 occurrence should be monitored post-vaccination in case of type replacement. Conclusive signs of HPV type replacement absence/occurrence up to 9 years post-vaccination is not yet observed, continued monitoring is needed.

#0558

5 - HPV prophylactic vaccines

Ecology of HPV types and subtypes in the pre- and post-vaccinated era

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Background/Objectives: The current large-scale HPV vaccine implementation will change the historical ecological conditions of the virus-human interaction, as for the first time a worldwide age cohort of vaccinated girls will possess a strongly protective immune response and subsequent herd effect, preventing infection by the most prevalent oncogenic HPVs. But the ability of viruses to survive through such evolutionary test is the combination of large population size and extant diversity. In the case of globally circulating HPVs, their population size is very large, with virtually all humans being effective carriers. Furthermore, oncogenic potential is not homogenous among or within HPV types, and the viral diversity exhibits some geographic structure. This dynamic virus-host interplay warrants monitoring of possible vaccine induced evolutionary responses of the viruses. Hence, we aimed to explore the changes in community structure and diversity of oncogenic HPV types in pre- and post-vaccinated environments.

Methods: Shifts in community structure of oncogenic HPV types between pre- and post-vaccinated environments were explored using multivariate models and graphical independence network analysis, and applied to available community randomized clinical trial HPV vaccination data1. In parallel, the community structure of oncogenic HPV types worldwide among unvaccinated women with normal cytology was estimated. Finally, viral population structure in deep time was inferred for particular oncogenic HPV types.

Results: Distinct community structure differences were observed between world regions among unvaccinated women with normal cytology. Subsequently, and apart from vaccine targeted HPVs, limited community structure differences were estimated post-vaccinated. Finally, and in agreement with previous reports, restricted within type population structure variations in deep time were observed.

Conclusions: Standing population structure and no vaccine induced evolutionary responses were observed for oncogenic HPVs. Nevertheless, the HPVs oncogenic potential seems to depend, at least partly, on the combination of virus and host genetic ancestry and warrants further monitoring post-vaccinated.

References: 1 Gray P, Palmroth J, Luostarinen T, Apter D, Dubin G, Garnett G et al. Evaluation of HPV type-replacement in unvaccinated and vaccinated adolescent females-Post-hoc analysis of a community-randomized clinical trial (II). Int J Cancer 2018. doi:10.1002/ijc.31281.

#0209

2 - Epidemiology and natural history

Human papillomavirus genotype replacement: still too early to tell?

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Background/Objectives: Although human papillomavirus (HPV) vaccines are highly efficacious in protecting against HPV infections and related diseases, vaccination may trigger replacement by genotypes not targeted by the vaccines if these types compete with the types that are targeted. So far, HPV genotype replacement is considered to be unlikely, based on the lack of systematic increases in the prevalence of the non-vaccine types in the first ten years following vaccination, and on the presence of cross-protection for some non-vaccine types. However, it is unclear whether these observations rule out type replacement in the long run.

Methods: To investigate to what extent type replacement can be inferred from early post-vaccination surveillance data, we constructed a transmission model to simulate the impact of vaccination. The model consists of two HPV types, a vaccine type and a non-vaccine type, which compete through infection-induced cross-immunity. We simulated vaccination scenarios for different levels of infection-induced cross-immunity and vaccine-induced cross-protection to the non-vaccine type. We derived measures used to evaluate type replacement in real-life early post-vaccination surveillance and validated whether these measures were able to correctly indicate type replacement in the post-vaccination equilibrium.

Results: Type replacement results from a balance between infection-induced cross-immunity (competition) and vaccine-induced cross-protection. In the absence of cross-protection, cross-immunity would lead to type replacement, but it could be prevented if cross-protection were strong enough. In the presence of weak cross-protection, non-vaccine-type prevalence may first decrease before rebounding into type replacement, exhibiting a honeymoon period of vaccination. Of importance, we found that vaccine effectiveness for non-vaccine types is an inadequate indicator for type replacement.

Conclusions: Although post-vaccination surveillance thus far has been reassuring, a decade of follow-up period may be still too short to detect or rule out type replacement. Monitoring of non-vaccine-type transmission remains pivotal in gauging the population-level impact of HPV vaccination.

SS 05 - Total protection and durability of the HPV vaccines

#0744

5 - HPV prophylactic vaccines

Durable Cross-Protection Afforded by Different Schedules of the Bivalent HPV Vaccine: the Costa Rica HPV Vaccine Trial

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Background/Objectives: Previously, the Costa Rica HPV Vaccine Trial (CVT) has documented cross-protection of the bivalent HPV vaccine against HPV31/33/45 up to seven years after vaccination, even with one dose of the vaccine. However, the durability of such protection remains unknown. Here, we evaluate different schedules of the vaccine's efficacy against HPV31/33/45 out to 11 years post-vaccination, expanding to other non-targeted HPV types.

Methods: We compared the rates of HPV infection in vaccinated women to the rates in a comparable cohort of unvaccinated women. We estimated the average vaccine efficacy (VEavg) against incident infections and tested for a change in VE over time.

Results: Among 3-dose women, we observed significant cross-protection against HPV31/33/45 (VEavg= 64.4%, 95%CI: 57.7 to 70.0%). Additionally, we observed statistically significant cross-protection against HPV35 (VEavg= 23.2%, 95%CI: 0.3 to 40.8%) and HPV58 (VEavg=21.2%, 95%CI: 4.2 to 35.3%). There was no decrease in VE over time (p-for-trend>0.05 for HPV31, 33, 35, 45, 58). As a benchmark, VEavg against HPV16/18 was 82.0% (95%CI: 77.3 to 85.7%). Among 1-dose women, we observed comparable efficacy against HPV31/33/45 (VEavg= 54.4%, 95%CI: 21.0 to 73.7%). Acquisition of non-protected HPV types was similar between vaccinated and unvaccinated women, indicating that the difference in HPV infection rates was not attributable to differential genital HPV exposure.

Conclusions: Substantial cross-protection afforded by the bivalent vaccine against HPV31/33/45 and, to a lesser extent, HPV35 and HPV58, was sustained and remained stable after 11 years post-vaccination, reinforcing the notion that the vaccine is an effective option for protection against HPV-associated cancers.

#0619

5 - HPV prophylactic vaccines

Bivalent HPV vaccine effectiveness in a real-world setting

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Background/Objectives: Following the successful clinical trials of hr-HPV vaccines, HPV immunisation has been introduced progressively across the world since 2007. Scotland, in common with the rest of the UK, introduced free-of-charge routine and catch-up immunisation in 2008 using Cervarix® (the "bivalent' vaccine). Routine immunisation was given to girls aged 12/13 years via a school-based programme, with uptake that has consistently been above 80%. Catch-up immunisation, administered through schools and through primary care, was offered to older girls still in school or who had just left school, up to the age of 18 years. Uptake in this group was 66% overall, and was higher for girls still at school than for those who had left school. The vaccine offered to girls was changed to the quadrivalent vaccine in 2012, and vaccination is being extended to boys in 2019. Scotland introduced a comprehensive immunisation surveillance programme that takes advantage of the comprehensive data linkage facilities between Scottish health data sets, the presence of a reference laboratory able to undertake extended HPV testing, and a Health Protection agency with a remit that included immunisation surveillance. As a result, a comprehensive picture of the effectiveness of Cervarix® in a real-world setting has emerged.

Methods: n/a

Results: It is possible to develop and maintain high vaccine coverage with the appropriate organisational and policy support in the face of anti-vaccine campaigns. The protective effect of the vaccine, even in women probably already exposed to HPV and in those not immunised as a result of herd protection, has been demonstrated both virologically and clinically at initial screen aged 20 and over a follow-up following onset of screening of between 4 and 9 years. The effect of HPV immunisation on the cervical screening programme and on colposcopy services has also been demonstrated. The publications and new data describing these effects will be summarised and the implications for cervical cancer prevention discussed.

Conclusions: n/a

References: Potts A et al 2013 Eurosurveillance 18: pii20593: Sinka K et al 2014 J Epidemiol Comm Health 68: 57-63 Kavanagh K et al 2014 Br J Cancer 110: 2804-11 Pollock K et al 2014 Br J Cancer 111: 1824-1830 Drolet M et al 2015 Lancet Infect Dis 15: 565-580 Cameron R et al 2016 Emerg Infect Dis 22: 56-64 Palmer T et al 2016 Br J Cancer 114: 576-81 Palmer T et al 2016 Br J Cancer 114: 582-9 Cruickshank M et al, 2017 Br J Obstet Gynecol 124: 1386-93 Munro A et al 2017 Br J Obstet Gynecol 124: 1394-1401 Kavanagh K et al 2017 Lancet Infect Dis 17: 1293-1302 Palmer T et al 2019 Br Med J 365: |1161

#1050

24 - Cervical neoplasia

LONG-TERM PROTECTION OF QUADRIVALENT HPV VACCINE AGAINST HISTOLOGIC HPV 16/18 CERVICAL PRECANCERS AND EFFECTIVENESS IN A REAL-WORLD SETTING

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Background/Objectives: Phase 3 trials showed efficacy against vaccine-targeted HPV infection and disease such as CIN2+. The real-world impact and effectiveness (VE) of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease was previously assessed in 2016, ten years after 4vHPV licensure. Our objective was to update the evidence related to impact and VE of 4vHPV vaccine on cervical abnormalities, including histologically-confirmed cervical intraepithelial neoplasia grade 2 and above (CIN2+), plus long-term follow-up [LTFU] of vaccinees in Nordic countries [1].

Methods: Medline/Embase were systematically searched for full-text, original articles published in English from March 2016-February 2019 on observational studies evaluating real-life benefits of 4vHPV vaccine. Reviews, conference presentations, modeling studies, and clinical trials were excluded. Impact was defined as population prevented fraction of abnormalities by comparing population pre and post vaccination program or trends over time and VE as proportion of prevented abnormalities comparing vaccinated and unvaccinated individuals. Publications reporting CIN2+ as an outcome are summarized in this presentation.

Results: During the 3-year search period, 10 publications reported impact or VE on CIN2+, compared to 13 publications from the prior 10 year review [2]. Studies reporting impact or VE on CIN2+ were published in Australia (2 impact) and the United States (5 impact, 3 VE). In Australia, the incidence of CIN2+ decreased by 43% in 20-24 year olds between 2004-2013, 6 years after 4vHPV introduction. Catch-up cohorts in Australia also benefited from vaccination, illustrated by a 17% decrease in CIN2+ in women age 25-29 who were vaccinated at age 18-26 years old. In the first study analyzing impact on invasive cervical cancer in the United States using NHANES data, a 29% reduction in incidence was observed in 15-24 year olds between 2003-2014, 7 years after 4vHPV introduction. The incidence of CIN2+ decreased by 39% in 20-24 year olds in New Mexico (2007-14), 50-74% in 21-24 year olds in Connecticut (2008-15), and 39.8% in 20-24-year-old insured females in the US (2007-14). Within VE studies conducted in the United States, relative risk reductions between vaccinated and unvaccinated populations ranged from 38-56% among females vaccinated before age 18. Vaccine efficacy for Nordic LTFU (14 years) was 100% [1].

Conclusions: Growing evidence on the impact and VE of 4vHPV vaccine on CIN2+ demonstrates significant reductions in cervical disease attributable to the vaccine, including new evidence on the benefits of vaccinating catch-up cohorts and early data on the impact on invasive cervical cancer.

References: [1] Kjaer, Susanne K., Mari Nygård, Joakim Dillner, J. Brooke Marshall, David Radley, Meng Li, Christian Munk et al. "A 12-year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 Nordic countries." Clinical Infectious Diseases 66, no. 3 (2017): 339-345. [2] Garland SM, Kjaer SK, Muñoz N, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clin Infect Dis. 2016;63(4):519-527.

SS 07 - First void urine as a biomarker source for primary and secondary cancer prevention

#0479

10 - Self-sampling

The rational and potential of using urine samples in cervical cancer screening and HPV vaccination programs.

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Background/Objectives: Today more interest is being directed towards the use of self-sampling methods. During this workshop we will discuss recent developments and achievements with first-void urine as biomarker source for primary and secondary cancer prevention. It should be noted that not the urine itself is of interest, but the potential HPV containing mucus and debris from exfoliated cells from the female genital organs (including the cervix), which are captured with the urine flow. Indeed, as each bodily cavity the genital tract is covered with mucosa consisting of epithelial cells where the upper layers are pushed off into the lumen. Papanicolaou already indicated in 1943 that superficial cell layers of a uterus carcinoma are exfoliated and subsequently mixed with secretions of the uterus and cervix, which make their way to the vagina and hence can be recognized in vaginal fluid smears. These cervico-vaginal secretions accumulate around the urethra opening, between the small labia, and are washed away with the initial urine flow. Consequently, this initial flow of urine - defined as first-void urine - collects most of this debris and contains more human and HPV DNA than random or mid-stream urine. Over the years, enhancements regarding the collection, storage and processing of urine for HPV detection have been identified. This has resulted in an increase in the number of studies publishing evidence of equivalent sensitivity of urinary HPV testing to both self-collected and clinician-obtained cervical samples, when performed using sensitive PCR-based tests. During this workshop evidence from urine-based HPV vaccination impact monitoring surveys will be presented as well as the outcome of other biomarker studies using first-void urine. Interestingly, a recent study conducted by Van Keer et al. confirmed that vaccine-induced HPV antibodies are detectable in the first-void urine of young women. The study showed significant positive correlations between HPV6/11/16/18-antibodies in first-void urine and paired sera. Based on the same concept for identifying HPV DNA and other biomarkers in first-void urine, the latter seems to also harbor HPV antibodies from serum transudate; previously nicely demonstrated in cervico-vaginal secretions collected by e.g. vaginal swabs or tampons. The fetal Fc receptor, present in the female genital tract, may play an important role in the presence of IgGs. Urinary testing could offer a non-invasive, more accessible and acceptable sampling method in primary and secondary cervical cancer prevention. We hope the selected presentations in this workshop help to appreciate the potential of this sample.

Methods:

Results:

Conclusions:

References:

#0627

5 - HPV prophylactic vaccines

USE OF HPV DNA IN URINE FOR FOLLOW-UP OF HPV VACCINATION. IMPACT DATA FROM RWANDA AND BHUTAN

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Background/Objectives: Rwanda and Bhutan were the first two low/middle-income countries (LMICs) to implement national human papillomavirus (HPV) vaccination. Both programs used quadrivalent vaccine against HPV6/11/16/18 and were primarily school-based.

Methods: HPV prevalence was estimated in schools by urine-based surveys in years 2013/14 and 2017 in both countries. We estimated vaccination effectiveness using increasinglyspecific criteria for selecting comparison groups based upon reported vaccination status.

Results: In Rwanda, 912 and 1087 participants from baseline and repeat surveys, respectively, were included in final analyses, and in Bhutan, 973 and 909 participants. The overall adjusted vaccine effectiveness (irrespective of reported vaccination status)against vaccine-targeted HPV types was78% (95%CI 51-90) in Rwanda and 88% (6-99) in Bhutan. Restricted effectiveness (assessed against unvaccinated baseline participants only), increased to 86% (69-94) and 97% (63-100), respectively. Overall effectiveness against other alpha-9 typeswas 59% (23-78) in Rwanda and 65% (32-83) in Bhutan, respectively. No impact against other HPV types was detectable.

Conclusions: In school attenders in both countries, prevalence of vaccine-targeted HPV types has decreased significantly, as well as that of other alpha-9 types, showing cross-protection. This provides the first direct evidence from LMICs of the marked effectiveness of a high-coverage school-based national HPV vaccination program.

#0485

5 - HPV prophylactic vaccines

Detection of HPV vaccine-induced antibodies originating from cervicovaginal secretions in first-void urine

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Background/Objectives: Monitoring HPV antibodies non-invasively would be a major advantage, particularly in studies that assess the impact of large-scale vaccination or in settings in which blood sampling is difficult. Several studies examining vaccine-induced HPV-specific antibody (HPV-Ab) levels in female genital secretions have shown moderate to good correlation between titres in cervicovaginal secretions (CVS) and serum. This study investigated the presence of vaccine-induced HPV-Abs, originating from cervicovaginal secretions (CVS), in first-void (FV) urine of (un)vaccinated subjects and the agreement with paired sera.

Methods: In this case-control study, 55 paired FV urine and serum samples were included from 19- to 26-year-old women, unvaccinated (n=19) or vaccinated (n=36) with the bi- or quadrivalent HPV vaccine during adolescence (collection between November-December 2015, trial registration ID: NCT02714114). Human IgA/G and HPV-Ab against HPV6/11/16/18 were measured in paired samples using the BioPlex ProTM Human Isotyping Assay (Bio-Rad, USA) and glutathione S-transferase (GST)-L1-based immunoassay (GST-L1-MIA) respectively.

Results: Significant positive Spearman rank correlations (rs) were found in HPV-Ab levels between FV urine and serum (HPV6: rs=0.777; HPV11: rs=0.757; HPV16: rs=0.876; HPV18: rs=0.636 ($p<0.001$)). In both FV urine and serum, significantly higher HPV6/11/16/18 antibody levels were observed in vaccinated compared with unvaccinated women ($p\leq0.017$).

Conclusions: The present study provides the first proof that vaccine-induced HPV antibodies are detectable in first-void urine of young women. Nevertheless, additional studies will be required to further optimize and validate the detection of HPV-Abs non-invasively.

#0490

8 - HPV testing

VALHUDES: Validation of Human papillomavirus assays and collection devices for HPV testing on first-void urine samples

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Background/Objectives: Systematic reviews have concluded that high-risk (hr)HPV DNA testing using target-amplification tests is as accurate on vaginal self-samples as on clinician-taken specimens for the detection of cervical precancer. Yet, insufficient evidence is available for specific combinations of HPV assays and self-sampling procedures. Next to vaginal self-samples, one more promising specimen to collect biomarker containing cervicovaginal secretions is the initial stream of urine, defined as first-void urine. To date, little clinical evidence is available using (first-void) urine as a primary HPV test and the outcomes have been found to vary substantially. In these studies, urine collection may also have been suboptimal for the detection of HPV given recent evidence focusing on the collection of a first-void specimen, collected within a preservative which together has the potential to significantly enhance the sensitivity of hrHPV DNA detection in urine. The VALHUDES (Validation of Human Papillomavirus Assays and Collection Devices for Self-samples and Urine Samples) protocol is designed as a diagnostic test accuracy study that aims to compare the clinical sensitivity and specificity of particular hrHPV assay(s) on self-samples - vaginal self-samples and first-void-urine - collected in agreement with standardized protocols, with hrHPV testing on matched clinician-taken samples.

Methods: Paired first-void urine (home-collected), self-collected vaginal (collected at the clinic), and clinical-collected cervical samples are collected at five colposcopy centres including a total of 500 women (25-64 years) that are referred to colposcopy due to cervical abnormalities (NCT03064087, Arbyn, JCV 2018). 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. Primary HPV results of sample sets are obtained using the AML Riatol qPCR HPV genotyping assay.

Results: Interim results from at least 100 women will be presented at the conference. These include both analytic and clinical performance of Riatol qPCR HPV genotyping assay in paired first-void urine, and cervical outcomes with respect to histological disease verification.

Conclusions: Given empirical evidence that the relative accuracy of HPV-testing on self- versus 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.

#0622

12 - Molecular markers

Host cell DNA methylation markers for the detection of cervical cancer and CIN3 in urine

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Background/Objectives: Urine samples provide a potential alternative to physician-taken or self-collected cervical samples for cervical screening. Screening by primary hrHPV testing requires additional risk assessment (so-called triage) of hrHPV-positive women. Molecular markers, such as DNA methylation, have proven most valuable for triage when applied to cervical specimens. This study was set out to evaluate the feasibility of DNA methylation analysis in urine to detect cervical cancer and CIN3.

Methods: Urine, including first-void urine (FVU), were collected from cervical cancer patients, a referral population with a colposcopy guided biopsy, and female controls. DNA-extracts were analysed for host cell methylation markers by quantitative methylation-specific PCR (qMSP). For comparison paired cervical scrapes were collected from cancer patients.

Results: Comparative analysis in paired samples of cervical cancer patients showed a moderately to strongly correlation between methylation levels detected in cervical scrapes and urine (r=0.51-0.72). All markers were significantly increased in urine from cervical cancer patients compared to controls and showed a good discriminatory power for cervical cancer (AUC=0.74-0.89). A subset of markers also demonstrated significantly increased methylation leveIs in FVU urine of women with histologically confirmed CIN2/3.

Conclusions: Our results show the feasibility of cervical cancer and CIN2/3 detection by urine-based DNA methylation testing. Molecular testing on urine creates opportunities to increase both adequate referrals for follow-up and number of screening participants.

HN 06 - Molecular characterization / Emerging biomarkers of HPV positive OPSCC

#0589

1 - Viral and molecular biology

Single cell sequencing analysis of HPV positive OPSCC

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Background/Objectives: Despite advances in surgery, radiation, and chemotherapy, there have been few major advances in the diagnosis and management of head and neck cancer. Long considered a disease of smokers and drinkers, head and neck squamous cell carcinoma has largely been ignored in major research efforts. However, the identification of human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) as distinct disease entity has sparked significant scientific interest. Although prior studies have suggested that intra-tumoral heterogeneity in these tumors may contribute to poor patient outcomes and treatment response, the underlying basis of this heterogeneity has yet to be defined. We sought to define intra-tumoral heterogeneity in HPV+ oropharyngeal suqamous cell caricnoma using single cell sequencing techniques, thereby defining the subpopulations of malignant, stromal, and immune cells that may drive this unique disease.

Methods: We utilized droplet based single cell sequencing approaches (10X genomics) to characterize 16 patients with HPV+ OPSCC, of which 3 were HPV- and 13 were HPV+. Patient samples were collected from 2018-2019 at a single academic institution. Samples were dissociated enzymatically into single cell suspension then barcoded using the 10X Chromium system, with library preparation and Illumina sequencing thereafter. The identified sequences were mapped to the transcriptome of humans as well as HPV subtypes. Cells were then computationally assessed using standard clustering algorithms based on gene expression, particularly differential expression, thereby defining both normal and malignant epithelium as well as major cell types. Copy number alterrations were assessed for individual cells, while gene expression programs found across multiple tumors were combined to define metaprograms.

Results: Altogether, we identified over 60,000 cells of high quality that could be classified into distinct cell types. Among malignant cells, we appreciated metaprograms related to proliferation, epithelial-to-mesenchymal transition, stemness, and cellular senescence. We similarly defined the expression states of stromal and immune cells, in particular, identifying T-cells in diverse functional states. Based on copy number aberrations, we were able to idnetifying multiple simultaneously exissting clones present in the same tumor, a pattern which was fairly common. Interestingly, these cells mapped to distinct expression states, suggesting that genetic, transcriptional, and epigenetic heterogeneity may contribute to HPV+ OPSCC. In addition, analyses of normal epithelium surrounding these tumors revealed a striking degree of expression heterogeneity, suggesting that their may be penumbral effects around these tumors.

Conclusions: Our study represents one of the largest single cell analyses of head and neck cancer ever completed, offering comprehensive insights into HPV+ OPSCC. In addition, this dataset represents the first single cell analysis of an HPV-mediated human tumor set, providing novel insights into the biology of these distinct cancers. Together, our data highlight the exciting observations that are possible through single cell sequencing that may redefine diangostic and treatment algorithms in the clinical setting.

References: PLEASE NOTE: This abstract is submitted in reference to an invited speaker presentation -- H&N Forum. Session 5: Molecular characterization/emerging biomarkers of HPV positive OPSCC / December, 5 / 09:30 - 11:00 / Title: Single cell sequencing analysis of HPV positive OPSCC.

MSS 02 - New triage approaches for HPV-positive women, what is the evidence?

#0321

9 - HPV screening

THREE-YEAR CUMULATIVE INCIDENCE RATES OF CERVICAL NEOPLASIA DURING THE LONGITUDINAL PHASE OF THE ONCLARITY TRIAL STRATIFIED BY EXTENDED GENOTYPING

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Background/Objectives: Evidence suggests that human papillomavirus extended genotyping (HPV xGT ; beyond 16/18) is effective for risk stratification in women with negative for intraepithelial lesions or malignancies (NILM) cytology and for risk-based triage approaches for women with atypical squamous cells-undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL) cytology. Here, cumulative incidence rate (CIR) values for HPV xGT were calculated to determine the long-term (three-year) predictive value for cervical intraepithelial neoplasia, grade 3 or worse (≥CIN3).

Methods: Women (N=29,513) were screened and referred to colposcopy/biopsy based on ≥ASC-US cytology or an HPV(+) result (5% normal cytology and HPV(-) controls also referred) at baseline (BL). Hierarchical ranked absolute risk (AR) values at BL, associated with ≥CIN3, were calculated based on HPV xGT results. Women not treated for cervical disease were invited for yearly follow up and had colposcopies/biopsies and treatment per protocol. Colposcopy referrals at years one and two occurred based on cytology (≥ASC-US); all women received colposcopy at year three. Three-year CIR values, associated with ≥CIN3, were calculated based on HPV xGT results. Data analysis involved verification bias adjustment and resulted in projected numbers of positive screening results (i.e. HPV(+) result), ≥CIN3 cases, AR, and CIR from BL through year three.

Results: Following screening with the Onclarity assay, the total number of BL ≥CIN3 cases was 199 (AR: 5.3%). The three-year CIR associated with any HPV(+) result for ≥CIN3 was 7.5%. In the NILM population, three-year HPV xGT-stratified CIR values for ≥CIN3 were: any HPV(+)=4.4%, HPV16=11.9%, HPV31=9.0% , HPV18=4.4%, HPV33/58=2.9%, HPV52=2.3%, HPV45=2.8%, HPV35/39/68=1.6%, HPV51=1.0%, HPV56/59/66=0.3%, and HPV(-)=0.1%. In the ASC-US/LSIL (combined) population three-year stratified CIR values for ≥CIN3 were: any HPV(+)=8.6%, HPV16=22.3%, HPV31=13.8% , HPV18=6.6%, HPV33/58=3.7%, HPV52=6.3%, HPV45=2.1%, HPV35/39/68=5.2%, HPV51=8.6%, HPV56/59/66=0.0%, and HPV(-)=0.8%.

Conclusions: While the three-year CIR for ≥CIN3 associated with HPV16 and 31 exceeded the current, consensus USA risk threshold for colposcopy referral, the management of NILM associated with intermediate- or lower-risk GT results may shift based on evolving estimates or other clinical factors. HPV xGT identified multiple three-year CIR bands for ≥CIN3 in the ASC-US/LSIL population. A follow up period could preclude immediate colposcopy for ASC-US/LSIL cytology associated with the lowest-risk HPV GTs.

#0551

17 - Methylation

VIRAL METHYLATION

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Background/Objectives: Human papillomavirus (HPV) DNA methylation testing is a promising triage option for women testing HPV positive during cervical cancer screening. We have previously shown strong associations of CpG site methylation in HPV genes E2, L2, and L1 with cervical precancer and cancer for HPV types 16, 18, 31, and 45.

Methods: We have developed next-generation (NG) bisulfite sequencing assays that measure HPV DNA methylation in the E2, L2, and L1 genes from the 12 most carcinogenic HPV types for triage of HPV-positive women. Another well-established assay, the S5 DNA methylation classifier, measures DNA methylation in HPV16, 18, 31, and 33, combined with a host-gene methylation marker, EPB41L3.

Results: In a case-control study nested in a population of women undergoing screening at Kaiser Permanente Northern California, we demonstrated that HPV methylation is a general phenomenon marking the transition from HPV infection to cervical precancer for 12 high-risk HPV types. The S5 DNA methylation classifier has been evaluated in several studies, showing high sensitivity for cervical precancer and cancer detection. Our newly developed NG sequencing assay provides several levels of risk stratification, from pooled HPV detection, to individual genotyping, and type-specific methylation results. We are also developing a host gene methylation assay on the same platform and will combine the best host and viral methylation targets into a single parsimonious assay that provides optimal risk stratification for various applications in cervical cancer screening studies. Validation of this assay in large, population-based cohort studies from various settings, and testing in self-collected samples is ongoing.

Conclusions: HPV DNA methylation is a particularly attractive triage biomarker because it is objective, highly reproducible, and has the potential to provide unprecedented risk stratification from a single test. If amenable to self-sampling, a methylation triage test that permits reflex testing of HPV-positive specimens without requiring a second follow-up visit for a clinician collected sample would have significant impact in expanding coverage to high-quality cervical cancer screening and triage in both high-and low-resource settings.

#0399

12 - Molecular markers

Host DNA methylation and miRNA

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Background/Objectives: HPV-based cervical screening requires triage to identify women with clinically significant infection. Epigenetic changes in the host cell, such as DNA hypermethylation and deregulated microRNAs (miRNAs), have been implicated in the development of cervical cancer, and represent potential triage markers. We set out to discover and validate DNA methylation markers and miRNAs that can be used for triage of HPV-positive women.

Methods: Genome-wide DNA methylation profiles using the Infinium Methylation 450K Array and genome-wide miRNA expression profiles using small RNA sequencing (sRNA-Seq) were determined in HPV-positive self-samples of women with and without CIN3. Candidate markers were validated by methylation-specific PCR (qMSP) or qPCR, respectively, and the combination of both marker types was evaluated.

Results: Genome-wide DNA methylation profiling revealed 12 DNA methylation markers for CIN3 detection. Subsequent multiplex qMSP analysis of these markers yielded a 3-gene methylation classifier (ASCL1, LHX8, and ST6GALNAC5) with good clinical performance for CIN3 in both lavage and brush self-samples in the validation series. Importantly, all self-samples from women with cervical cancer scored DNA methylation-positive. Classification of sRNA-Seq data yielded a 9-miRNA marker panel. In a series of HPV-positive cervical scrapes, the combination of miRNA and DNA methylation analysis demonstrated complementarity. While a miRNA classifier seemed more predictive for CIN2, DNA methylation was particularly high in HPV16-positive and histologically more advanced CIN3.

Conclusions: Our studies show that both host cell DNA methylation and miRNA expression analysis offer promising novel molecular triage strategies for CIN3 and cervical cancer, applicable to both self-samples and cervical scrapes.

CS 02 - Risk and prevention of cervical cancers in post-menopausal women

#1036

22 - Diagnostic procedures / management

CLINICAL EXPERIENCE IN MANAGEMENT OF HPV-SCREENED BIRTH COHORTS PREVIOUSLY SCREENED WITH CYTOLOGY.

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Background/Objectives: Primary HPV screening is more sensitive for detecting cervical precancer and cancer than cytology. As a result, HPV testing is replacing cytology in many developed countries. At present, women aged 23-59 are still screened with cytology in Denmark; primary HPV screening is recommended in women aged 60-64. However, primary HPV screening is expected to replace cytology among women aged 30-64 in the near future. This will likely result in an increase in the referral rate to colposcopy. It is well known that the transformation zone is often retracted into the cervical canal in older women, resulting in inadequate colposcopy. It remains unclear how to manage screening-positive older women when disease is not initially found in the cervical punch biopsies, particularly if they are found to have persistent high-risk HPV positive results. Following the implementation of primary HPV screening much attention has been given toward minimizing the number of unnecessary colposcopies in order to do "less harm" through use of cytology and secondary triage biomarkers such as p16 and methylation. However, it is also important to take into account older women's preferences regarding screening, diagnostics, and treatment. In Denmark, studies have revealed that older women participating in screening prefer being treated without histologic confirmation of precancer, rather than risking underdiagnosis. Future studies should explore how to optimize diagnostics of cervical precancer and cancer in older women and how to best follow-up screen-positive women when disease is not initially found

Methods: na

Results: na

Conclusions: na

References: na

WF II - Dépistage HPV du cancer du col, nouvelles directions et mise en œuvre en période de transition

#1063

14 - Screening methods

QUEL DÉPISTAGE POUR LES FEMMES VACCINÉES?

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Background/Objectives: La vaccination contre le HPV et le programme de dépistage sont 2 entités liées. En effet, les facteurs qui influencent les décideurs dans le choix d'un futur programme de dépistage du cancer du col utérin sont multiples. L'évaluation des programmes de vaccination et du taux de vaccinées, le choix du test de dépistage et l'intervalle dans le dépistage représentent les facteurs les plus importants pour la prise de décision. L'augmentation de l'intervalle entre les dépistages et la modification des âges pour le début et la fin du programme de dépistage sont deux éléments significatifs reliés à la vaccination et aux programmes de dépistage.

Methods: D'après une méta- analyse de Drolet et al, le taux de succès des programmes de vaccination dans les pays avec multi-cohortes et avec taux de vaccination de plus de 50% est remarquable avec une baisse de CIN2+ de 51% à 31% après 5 à 8 ans de la vaccination selon les cohortes d'âge de 15-19 ans et de 20-24 ans.

Results: Le vaccin HPV9 augmente la couverture vaccinale pour 5 types additionnels de virus oncogènes. Le dépistage primaire par test du HPV diminue le risque à vie de cancer du col de 18%. Si on combine le dépistage par HPV avec le vaccin HPV9, la diminution sera de 83% sur le risque à vie de développer un cancer du col. Avec de faible risque de cancer du col associé aux 2 techniques dépistage et vaccination, il devient essentiel d'envisager des intervalles plus longs et une réduction du nombre de dépistage à vie pour la population vaccinée. De plus, le peu d'anomalies cytologiques démontrées chez les femmes vaccinées par le vaccin HPV9 renforce la notion d'une possible perte d'expertise des cytologistes en raison d'une faible exposition aux anomalies.

Conclusions: Une étude par modélisation analysant 4 pays développés, nous démontre qu'avec la vaccination par le vaccin HPV9, de 2 à 5 dépistages au cours de la vie des femmes seraient nécessaires en fonction de leurs coûts de santé et de leur « willingess-to pay ». En dernier lieu, d'après une étude australienne en vue de l'élimination du cancer du col par la vaccination et le dépistage combiné, il est plausible d'envisager l'élimination du cancer du col pouvant être atteint en 2080, avec un taux < 2 / 100,000 pour toutes les tranches d'âge.

#0590

9 - HPV screening

Workshop: Dépistage HPV du cancer du col, nouvelles directions et mise en œuvre en période de transition. Presentation: Questions to be resolved for implementation of HPV screening

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Background/Objectives: HPV-based screening is recommended for women over 30-35 by European guidelines (von Karsa 2015). Implementation of HPV-based screening is not just replacing Pap test with HPV test, but it implies deep changes in screening algorithms, organization of clinics and laboratories, communication and culture of health personnel.

Methods: To implement an HPV-based screening we must choose the best algorithm for our context among those proposed by the European guidelines. Compared to Pap test, HPV test is less specific. Proportion of women positive to HPV test is too high and HPV-positive women have a too low prevalence of CIN2+ to be directly referred to colposcopy. Cytology triage is recommended. While women with high-grade cytology are immediately referred to colposcopy, and women with negative cytology are referred to re-testing, how to manage ASC-US and L-SIL cytology should be decided according to the prevalence of CIN2+ in these women and to local preferences and acceptability. The same is true for how and when retesting HPV-positive/cytology-negative women: the most commonly adopted strategies are cytology after 6 months and HPV after one year. For triaging women without a second appointment, we need a sampling viable for both molecular and cytological tests. Even if collection of two samples at the first appointment is possible, almost all ongoing programs adopted liquid based cytology. Shifting to liquid based cytology and dramatic increase in the prevalence of disease in HPV-positive compared to general population require re-training of cytologists. HPV-negative women should be re-screened at least after 5-years. In organized programs, changing from 3-year to 5-year interval requires to re-schedule the target population to be screened. If we do not take into account this issue, the result would be a large difference in service workload in the next round with two years with almost no screening activity and three years with very intensive activity, that is a non-optimal use of resource. The shift to a molecular test, which requires more technology costs and lower human resources than Pap test, favors the centralization of labs. Centralization is also functional to maintain adequate volumes of slides per readers, because the number of Pap test will diminish dramatically. HPV-based screening

Results:

Conclusions: Finally, the complexity of the protocol, the length of the interval, the need to know previous examination results in order to correctly manage the women, and the centralization of labs are all factors that strongly push in the direction of well-organized programs, while the opportunistic approach is not recommended.

References: von Karsa L, Arbyn M, H, Dillner J, Dillner L, Franceschi S, Patnick J, Ronco G, Segnan N, Suonio E, Törnberg S, Anttila A. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus research 2015;1:22-31

HN 07 - HPV and RRP: confronting the challenge of a rare disease

#1059

29 - HPV and oropharynx / Head and neck cancer

Clinical consensus building for the use of systemic Avastin in RRP

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Background/Objectives: To provide recommendations to otolaryngologists and allied physicians for the use of systemic bevacizumab(Avastin) to treat Recurrent Respiratory Papillotomous(RRP).

Methods: A three-iterative delphi method questionnaire was used to establish expert recommendations by panelists made up of mainly pediatric otolaryngologists but also included adult otolaryngologists and laryngologists as well as both adult and pediatric hematologist-oncologists and oncologists, pediatric infectious disease pediatricians, pediatric surgeon on patient characteristics, disease characteristics, treating center characteristics, prior treatment characteristics and prior work-up.

Results: Sixty-three members completed the survey. Of all the items that were listed, a total of 60 items met consensus criteria and 12 items met near-consensus criteria. A preliminary review of these recommendations along with case examples will be discussed.

Conclusions: Systemic bevacizumab(Avastin) consensus recommendations are aimed at improving patient-centered care in patients with Recurrent Respiratory Papillotomous (RRP).

MSS 03 - Pro/Con session - hot topics

#1040

8 - HPV testing

HPV-NEGATIVE CERVICAL CANCERS ARE THEY WORSE CLINICALLY? YES

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Background/Objectives: The problem of HPV negativity in cervical cancer is complex. It is particularly and mainly a problem of cervical adenocarcinoma. In large epidemiological studies HPV negativity rates of up to 30% are seen in these cancers. We have studied this in detail in a global study, and in Europe and China. There are several reasons for HPV-negativity, and all of these contribute to a poor outcome for patients with HPV negative adenocarcinoma presenting at the cervix. The first issue is that of HPV testing. Some clinical HPV tests, including HC2, are not always positive even if the tumour itself contains HPV. This is a matter of test sensitivity, but even using a very sensitive testing algorithm on tissue samples, including testing for HPV E6/7 genes at the level of one copy per cancer cell in selected pure cancer samples, some adenocarcinomas presenting and managed as cervical cancers remain HPV-negative. One important cause of this is pathological misdiagnosis leading to inappropriate treatment. This is particularly important when pathological resources and expertise are limited and when only a biopsy specimen is available and accounts for some of the discrepancies between countries and studies. The most important of several misdiagnoses is endometrial cancer and there are also other uterine tumours, and occasional metastases from elsewhere. Molecular and pathological investigation also show that in Asia (especially Japan) the frequency of gastric type cervical adenocarcinoma is an important issue, although it is less common in the West. Pathologically this is a difficult diagnosis against a well-differentiated usual cervical adenocarcinoma, most of which are driven by HPV. Gastric type cervical adenocarcinoma is often associated with germline and sporadic STK11 mutations and has a bad prognosis. Studies have also shown some late stage cervical adenocarcinomas classified by expert review as usual type are HPV-negative and show somatic tumorigenic mutations including p53 mutations. Whether these are tumours that were initiated by HPV or represent something similar to gastric type cervical adenocarcinoma with a completely separate pathway is unclear. HPV negative adenocarcinoma presenting at the cervix and true HPV-negative cervical adenocarcinoma certainly occur and are real issues but it is an infrequent issue (<2% of all cervical cancer) and is no excuse for not employing and relying on appropriately sensitive hrHPV testing in primary cervical screening.

Methods:

Results:

Conclusions:

#0386

2 - Epidemiology and natural history

SHOULD WOMEN OVER 65 EXIT CERVICAL CANCER SCREENING? - YES

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Background/Objectives: The recommended age at which to stop cervical cancer screening generally varies between 50-70 years worldwide, but these recommendations are generally based on low quality evidence on the effectiveness of screening in older women. Due to ageing populations in many countries and the WHO call to action to eliminate cervical cancer as a public health problem, there is likely to be renewed interest in screening older women for cervical cancer.

Methods: Review of litterature supporting at which age to stop cervical cancer screening, supplemented by decision modeling analyses.

Results: While cervical cancer mortality rates increase with age and while there is evidence that screening does prevent cancer at older ages, there are ethical and practical reasons why screening women over 65 may not be desirable. These are framed in terms of the balance of benefits and harms of screening at this age. The benefits of screening generally decrease with age: 1) the absolute remaining lifetime risk of cervical cancer declines with age, especially in HPV-negative women 2) potential gains in life expectancy from screening diminish after age 65, and 3) the estimated preventive efficacy of screening at older ages is likely overestimated due to confounding in many studies: women who continue screening at older ages are more likely to have been screened at younger ages. Conversely, the potential harms from screening procedures and positive test results (anxiety, physical pain) persist at older ages. Continued screening of repeat screen-negative women is also likely not cost-effective due to their low cervical cancer risk, and screening programs in limited resource settings would have more public health impact from prioritizing screening at younger ages (30-50). Recommendations to stop screening in certain age groups may be met with negative public backlash due to a lack of public awareness of the potential harms of screening. This might be mitigated through better communication of screening harms and benefits with age.

Conclusions: The age at which the risk of cervical cancer becomes too low to be worth the potential harms from screening has no definitive answer and depends on societies' and individuals' risk tolerance and available resources.

HN 08 - HPV and oropharynx / Head & Neck cancer (submitted papers)

#0108

29 - HPV and oropharynx / Head and neck cancer

Role of latent Infection in HPV induced disease of the Head and Neck

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Background/Objectives: HPV causes both benign and malignant tumors in the head and neck. The immune system is key to the controlling or eliminating HPV infection. HPV6/11 causes recurrent respiratory papillomatosis (RRP) and HPV16 causes tonsil/oropharyngeal cancer. The prevalence of both RRP and oropharyngeal cancer is approximately 2/100,000. Despite multiple therapies for RRP including; photodynamic therapy, Interferon, and COX-2 inhibitors. We have found that HPV persists in clinically normal airway tissues. Including those that were in clinical remission. Most recently we have asked if a similar situation exists for HPV 16 induced tonsil cancer.HPV16 causes most oropharyngeal cancers. Others have reported very low prevalence of HPV16 in normal tonsils, although it is readily detected in the oral cavity. This suggests that HPV infection of tonsils is normally cleared rapidly by the immune system in healthy individuals.

Methods: We asked whether HPV was present in clinically normal contralateral tissues of patients with HPV+ oropharyngeal cancer. Total DNA and RNA were extracted from paired biopsies from 16 patients in New York and 16 in Rome. The New York samples were analyzed for HPV 16 by qPCR, the Rome samples analyzed by PCR followed by direct sequencing for genotyping. All RNAs were analyzed by qRT-PCR using primers within E7.

Results: Twenty-five tumors were positive for HPV (78%); one tumor contained HPV18. Fourteen patients (43.8%) had HPV16 in their contralateral normal tissues. Five patients with HPV16+ tumors had two normal tissue biopsies, and at least one was positive in each case. The HPV copy number was much lower than in the tumors (0.02- 0.1 compared to 1-10 copies/cell), suggesting that only a subset of normal cells was infected. HPV-E7 mRNA was present in the tumors but undetectable in all the normal tissues, consistent with latent infection and not tumor spread.

Conclusions: Latent HPV16 on 11/6 is widely present in that subset of individuals whose immune system has specific defect that is unable to recognize this group of viruses. These patients remain at risk of recurrent disease despite all current therapies.

#0452

29 - HPV and oropharynx / Head and neck cancer

A Simple, Rapid, Multiplex, Isothermal Amplification Assay for Detection and Genotyping of Human Papillomaviruses in Formalin-Fixed Paraffin-Embedded Tissues

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Background/Objectives: Rapid and accurate detection and identification of human papillomavirus (HPV) is important for both clinical management and population screening. Detection of HPV DNA from formalin-fixed paraffin-embedded (FFPE) specimens has been a challenge as it usually requires lengthy and inefficient sample process. The AmpFire HPV assay (Atila Biosystems Inc, Mountain View, CA, USA) incorporates a multiplex isothermal amplification to detect and genotype 15 high-risk (HR) HPV genotypes directly from raw samples without needing to extract or purify the DNA. The whole detection process requires couple pipetting steps and can be completed within 2.5 hours.

Methods: We performed analytic and clinical validation of AmpFire Multiplex HPV assays on FFPE cervix/vulva and oropharynx diagnostic tissue samples. The performance of the AmpFire assays in clinical samples was evaluated using 214 FFPE specimens.

Results: Limits of detection determined by plasmids cloned with HPV genotype-specific sequences were 2 copies/reaction for HPV16, HPV18, and some HR HPV genotypes, and 20 copies/reaction for the remaining HR HPV genotypes. The performance of the AmpFire assays in clinical samples was evaluated using 214 FFPE specimens. The AmpFire assay failed in one clinical specimen for an invalid rate of 0.5%. The AmpFire assay detected HPV in clinical samples with positive percent agreements of 100.0% for HPV16, 100.0% for HPV18, and 94.7% for non-16/18 HR-HPV, and 100% negative percent agreements for HPV16, HPV18 and non-16/18 HR-HPV. Qualitative detection agreement was obtained in the reproducibility study.

Conclusions: In summary, the Atila AmpFire HPV assay demonstrated excellent analytic sensitivity and specificity for detection and genotyping of 15 HR HPV genotypes. Assay parameters of simple specimen processing, small sample size requirement, rapid turnaround time and being near instrument-free render it well suited for HPV detection and genotyping in FFPE specimens.

#0518

29 - HPV and oropharynx / Head and neck cancer

HPV-capture in oropharyngeal squamous cell carcinoma : is episomal HPV16 a marker of bad prognosis?

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Background/Objectives: HPV-positive oropharyngeal squamous cell carcinoma (HPV-OPSCC) constitute a tumor entity with better prognosis. However, appropriate selection of patients for better treatment management is critical and biomarkers are strongly needed to ultra-classify these HPV-OPSCC. Recently, a new approach based on HPV-capture (Capt-HPV) coupled with next generation sequencing (NGS) identified HPV molecular signatures in cervical cancers(Holmes et al., 2016). Primary results suggested that poor outcome could be associated to these signatures. Herein, we described HPV molecular characteristics obtained with Capt-HPV in a cohort of HPV16 OPSCC from European Georges Pompidou Hospital (EGPH) and their correlation with clinical data.

Methods: A cohort of HPV16-positive OPSCC (p16INK4A and HPV16 DNA positive) was prospectively collected and analyzed with Capt-HPV coupled with NGS allowing the detection of 208 variants from 88 HPV genotypes. DNA was extracted from frozen tumoral biopsies and sequencing was performed with an Illumina Miseq instrument. Data were automatically analyzed using a specific pipeline developed by the EGPH biomedical informatics team. HPV genotyping, HPV full length sequence, HPV molecular status (episomal or integrated), and positions of HPV/human junctions were obtained. Clinical data were extracted from the EGPH clinical data warehouse.

Results: Tumor samples from 54 patients were analyzed. A majority (n=35, 65%) presented strictly episomal forms of HPV16. HPV16 integration was reported in 19 patients (35%) for whom 9 presented strictly integrated HPV forms and 10 were a mixture of integrated and episomal forms. Multiple HPV16/human genome junctions were detected in 2 samples. Integration occurred in human genes for 74% (n=14) of patients with integrated HPV. Six of these 14 genes are associated with carcinogenic process and 2 are reported to facilitate metastasis. Four patients had integrations in non-coding regions, and we couldn't assess the precise human site of integration for 1 patient. Moreover, complete sequences of E6 and/or E7 oncogenes were observed in all the samples. E2 gene was impacted for 68% (n=13) of patients with integration. Interestingly, 3 of the 4 integrations with conserved E2 gene were in a candidate gene (BCL3, SOX2-OT, CD274 (PDL1)). Complete deletion of E2 was observed in 5 patients. No correlation between the integration status of HPV and the T/N/M status or the 2018 HPV OPSCC staging of the tumor was observed. However all the patients with integrated forms of HPV16 were N+ while 5 patients with strictly episomal forms of HPV16 were N0. Strikingly, among the 4 patients that died from their cancer, all had a strictly episomal form of HPV16 although this association was not statistically significant (P=0.15) (see attached figure). None of the patients with integrated HPV16 had died at the time of the analysis.

Conclusions: Different HPV molecular signatures were observed in our HPV OPSCC cohort with a majority of episomal forms. Integration of HPV occurred frequently in genes involved in oncogenic and metastasis process. Further investigations on larger multicentric cohorts would allow confirming or not if there is an association between the integration status and the N status and, more importantly, if the patients with integrated forms of HPV have a better prognosis than the patients with episomal forms in order to improve OPSCC patient management.

#0596

8 - HPV testing

Association of HPV Infection and p16 Expression in Oral Cancer: A Multicenter Study in Thailand

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Background/Objectives: Oral cancer remains a major health problem worldwide including Thailand, with oral squamous cell carcinoma (OSCC) being the most common type (1, 2). Tobacco smoking/chewing, alcohol consumption, and betel quid chewing have long been established as classic risk factors for OSCC. However, many previous studies have shown that human papillomavirus (HPV) infection, particularly HPV types 16 and 18, may play a role in carcinogenesis of OSCC (3, 4). This study aimed to identify the prevalence of HPV 16 and 18 infections in patients with OSCC in Thailand and investigate the associations of p16 expression and HPV16/18 DNA with demographic and clinicopathologic parameters,and the classic risk behaviors of the patients.

Methods: We conducted a retrospective analysis of 403 formalin-fixed paraffin-embedded OSCC specimens collected during 1999-2019 from four centers in four different regions in Thailand, including Faculty of Dentistry, Chiang Mai University (northern region); Prince of Songkla University (southern region); Chulalongkorn University (central region); and Khonkaen University (northeastern region). p16 expression was assessed by immunohistochemistry (IHC). The detection of HPV16/18 DNA was performed using polymerase chain reaction (PCR). Descriptive statistics was used to analyze the demographic, clinicopathologic information, and the classic risk behaviors. The Cohen's kappa test was used to assess the inter-observer and intra-observer agreement in p16 scoring and the concordance between p16 IHC and HPV16/18 DNA PCR. The associations of p16 expression and HPV16/18 DNA with demographic, clinicopathologic, and classic risk behavior parameters were analyzed using Student's t-test (for the continuous variable) and Chi-square or Fisher's exact test (for the categorical variables). The results with p value less than 0.05 were considered significant.

Results: Of all OSCC specimens, p16 expression was observed in 67.5% (272 of 403 cases). DNA extracted from 172 of 403 specimens (42.7%) showed positive results for human beta-actin gene (internal control) and was subjected to HPV16/18 DNA detection by PCR. Overall, HPV16 and/or 18 DNA was detected in 8.1% (14 of 172). Among these, HPV18 DNA was found in 57.1% (8 of 14), HPV16 DNA in 14.3% (2 of 14), and HPV 16 and 18 DNA (co-infection) in 28.6% (4 of 14). The highest prevalence of HPV16/18 DNA was noted in the patients from the northern region (20.0%), followed by those from the southern region (6.9%). We did not detect HPV16/18 DNA in the specimens from central and northeastern centers. When p16 IHC and HPV16/18 DNA PCR were considered, 5.8% (10 of 172) were positive for both methods. The concordance of p16 IHC and HPV16/18 DNA PCR was poor (κ=.023, p=.485). p16 expression was significantly associated with the patients younger than 60 years (OR=1.60, 95% CI 1.03-2.55, p=.035). However, there were no significant associations between HPV 16/18 DNA and demographic, clinicopathologic, and the classic risk behavior parameters.

Conclusions: Our findings confirm HPV16 and 18 infections in a subset of Thai patients with OSCC. The highest prevalence of HPV16/18 DNA was seen among the patients from the northern region. Moreover, a poor agreement between p16 expression by IHC and HPV16/18 DNA detection by PCR was observed.Further studies on HPV-related sexual behaviors and survival outcomes with HPV-positive OSSC will provide better understanding of the role of HPV infection in oral cancer in Thai patients.

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#0090

28 - Oral HPV infection

Artificial Intelligence and oral brush sampling for microbiologic diagnosis in General Dental Practice, a new entity towards efficient explainable cytology.

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Background/Objectives: The incidence of oral cancer is higher than for cervical cancer with a poor survival rate especially when late discovery. Patients in Sweden go regularly to their general dental practioner (GDP) at the national dental service (NDS) or to a dentist in private practice and a robust screening program can without difficulty be implemented for early diagnosis and preventive measures. Our intention is to test and compare the outcome of non-invasive brush sampling between performers in general dental practice to a specialist in oral medicine.

Methods: Implementation of oral cancer screening will include 10 general dental practices in Sweden to compare the outcome from GDP with a specialist in oral medicine and further develop the AI software for the automated cytology process. Brush biopsies will be obtained from 200 patients with potentially malignant lesions (PML): oral lichen or oral leukoplakia and 200 individuals with healthy oral mucosa as controls. We have previously shown the non-invasive brush method to be safe and accurate in a specialist clinic in Sweden with 160 patients with documented oral cancer, PML or anogenital hrHPV lesions (1,3). The oral brush samples to be collected will be automated analysed for hrHPV with FTA elute micro card and automated cytology with Thin Prep liquid base. Patients with PML are referred to the specialist in oral medicine for repetitive sampling including a routine histological investigation. Results of both cytology and hrHPV DNA from the GDP and the specialist will be compared.

Results: Our results from our previous study of the automated screening cytology process showed the system to be reliable for classifying oral cells from brush sampling using AI based on deep learning and deep convolutional neural networks (1,2,4). Evalutation from a previous method study indicates that hrHPV will be detected with the same accuracy with the FTA microcard as with the liquid base method, Seegene Anyplex 28 (3). Based on our earlier findings we have started inclusion of patients in GDP with good progress.

Conclusions: The overall aim is to reduce the prevalence of oral cancer by introducing screening of high risk patients by dentists and dental hygienists in GDP in the NDS including intervention against tobacco habits and alcohol abuse. Screening for oral cancer and PML in GDP will identify patients at risk for developing oral cancer and those with potentially malignant cell changes at an early stage, thereby reduce the treatment burden and mortality.

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#0509

2 - Epidemiology and natural history

Estimating the Prevalence of Oropharyngeal Squamous Cell Carcinomas from Human Papilloma Virus status in the USA by combining Machine Learning with Bayesian Inverse Modelling

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Background/Objectives: Despite an epidemic increase in the prevalence of HPV related Oropharyngeal squamous cell carcinomas (OSCCs) in Northern America and parts of Europe, there is virtually no information about the natural history of these cancers. Nevertheless, it is likely that a subclinical oral HPV infection that persists for decades precedes the development of these cancers similar to cervical cancer. However, unlike cervical cancer which is preceded by well-defined histopathological pre-cancer grades, precursor lesions have not been identified for OPSCCs. The key parameters that govern natural history (transition from infection to malignancy) remain largely ill-defined for these cancers. Mathematical models have previously been successfully used to estimate some of these ill-defined parameters in cervical cancer and may find application in understanding the natural history of oral HPV infection and its role in driving Oropharyngeal carcinogenesis. Our objective therefore is to employ a mathematical modelling approach to estimate the conditional probability of developing OSCCs following an incident HPV infection and other co-factors.

Methods: The study population for data modeling was derived from the National Health and Nutrition Examination Survey (NHANES) and the SEER registry data. The NHANES data is stored in SAS format as a separate file for each group of variables and each period of the survey (2011-2012, 2013-2014). The files were imported into R and linked through the unique respondent ID. The variables used for analysis included: Gender, Age, Race/ethnicity, Education, Marital status, Poverty ratio, and Vaccinated HPV status. The SEER data was extracted from the specialised Head and Neck with HPV Status database. Machine learning and Bayesian approaches were employed to model the probability of developing OSCC following an incident HPV infection. To estimate the conditional probability we use a novel double-Bayesian method whereby a Bayesian machine learning model is first used to estimate the probability of HPV associated with OSCC (and covariates) from SEER data. This model is then inverted using Bayes' theorem again to reverse the probability relationship. The inversion involves corrections using incidence values which are obtained from both SEER and NHANES data.

Results: The data set contains 9439 subjects of which 6351 (67%) were HPV positive and 3088 (33%) negative. The training set contained 7079 subjects and the test set 2360, with similar proportions of HPV negative/positive as the full data set. The estimated probability of developing OSCC following an incident HPV infection was slightly higher for married white individuals than people of other ethnic origin. Interestingly, whilst the male estimates were all broadly similar, the estimated probability for females were quite different, especially for the Hispanic group who displayed lower rates of developing OPSCCs with age following an incident HPV infection.

Conclusions: We have employed a novel mathematical approach to infer the natural history of OSCC following a HPV infection, however considering the lack of longitudinal follwo-up data and other covariate information, we appreciate the limitations of this approach and at best recognise that this is a first guess estimate of a natural history model of HPV driven OSCCs.

#0818

2 - Epidemiology and natural history

ECHO [Epidemiology of HPV infection in Oral Cancer in Ireland]

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Background/Objectives: Head and Neck Squamous Cell Carcinomas (HNSCCs) are the sixth most common type of cancer worldwide. While the incidence of other HNSCCs decreased over the past two decades, correlating with decreased tobacco use, the age-adjusted incidence of oropharyngeal Squamous Cell Carcinoma (OSCC) increased in this same period. Human Papilloma Virus (HPV) is the core carcinogen proposed in the development of OSCCs. The aim of the ECHO study is to conduct for the first time a large population-based epidemiological study of the prevalence and incidence of HPV in oral cancers in Ireland.

Methods: The ECHO study is a retrospective study of HPV infection in oropharyngeal, laryngeal and oral cavity squamous cell carcinoma cases patients diagnosed between 1994 and 2013 in Ireland. A total of 3,415 eligible cases across 14 different hospital sites have been identified through the National Cancer Registry, Ireland. Following pathological review of the cases and selected blocks, FFPE tissue sections are processed and tested for 21 different HPV genotypes using a Multiplex PCR Assay based on the Luminex Platform developed by Massimo Tomassimo's group at the International Agency for Research on Cancer (IARC).

Results: A total of 861 primary oral (oropharyngeal, oral cavity, and laryngeal) SCC cases, identified through the National Cancer Registry, were obtained from hospitals across Ireland and tested for HPV DNA using Multiplex PCR Luminex technology based in and sanctioned by the International Agency for Research on Cancer (IARC). A prevalence of 17.1% HPV DNA positivity was detected in the study population. Prevalence in oropharyngeal cases was 41.1%; in oral cavity cases was 10.9%; and in laryngeal cases was 7.8%. High-risk carcinogenic HPV16 was the overwhelmingly dominant genotype amongst HPV positive cases regardless of sub-site. HPV-related oropharyngeal cases saw the highest average annual percentage change in incidence of 16.4% ($p<0.0001$) over the time period. Significant predictors of HPV positivity amongst oral SCC were younger age, oropharyngeal sub-site, and never- and ex-smoking status.

Conclusions: Cumulatively, these findings highlight the importance of introducing boys in to the national HPV vaccination programme in Ireland, and the relevance of the nona-valent Gardasil-9 vaccine to HNSCC prevention, two changes the Irish government implemented in September 2019.

#0703

28 - Oral HPV infection

Saliva testing head and neck cancer : detection of bacterial DNA, HPV and VOC in stabilized self collection kit Oncoral.

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Background/Objectives: Currently, the detection of oral cancer is currently often first recorded at a late stageand that survival does correlate negatively with stage of detection. We are proposing to globally analyze oral health from saliva. There is increasing interest in the potential offered by saliva biofluid-containing biomarkers such as bacteria, HPV, volatile organic compounds (VOCs), RNA, DNA mutation & methylation for improvements in the accurate detection and diagnoses of head and neck cancers. Direct contact between saliva and oral cancerous lesions renders the monitoring of tumor markers in salivary media an attractive alternative to tissue biopsy at early stage of cancer development. Saliva is not a mixture of secretions, gingival crevicular fluid containing microbiota (bacteria, viruses, fungi), metabolic products, epithelial cells. Several types of inflammatory biomarkers associated with oral cancer have been detected in saliva, and an increasing number with specific molecular (RNA, DNA), biochemical and infectious markers. Specific combinations of volatile organic compounds (VOCs) have already been found in saliva in many studies focused oral and systemic diseases and lung cancer. The objective of this work was to evaluate from the sample saliva sample, the ability to detect pathogenic bacteria , HPV and a unique combination of VOCs to distinguish head and neck cancer patients from a group of healthy control individuals.

Methods: Saliva was collected using 4 ml of a tartrazine solution before stabilization with sodium azide and ammonium sulfate as preservatives for metabolites (stable at room temperature for a period of up to 10 days). From stabilized saliva, parameters were controlled before the VOCs analysis: sample volume, raw saliva quantity and total bacterial DNA load following by DNA HPV analysis. VOCs abundances was measured by SPME-GC-MS analysis. For each sample, 78 molecules were investigated, and their abundances computed. From these 78 molecules, 1,767 molecular ratios were obtained. ANOVA was performed on these 1,767 ratios according to the factor "tumor", and was used to select significant ratios ($p < 0.05$). ANOVA and FDA were confirmed with Statistica software (StatSoft France).

Results: DNA was properly extracted from stabilized saliva. Bacterial DNA was measured at quantified (total count and specific pathogens). Cellularity of the sample was measure by Beta globin gene amplification with BD Viper kit and Sansure genotype kit. HPV was measured and absent of all our samples. The results of FDA gave a linear coefficient for 6 ratio (R1 to R6). The classification model with the 6 molecular ratios discriminated 93.75% of the samples according to the factor "tumor". Sensitivity was 92.5%, and the specificity was 95.8%.

Conclusions: Saliva was stabilized and used from the same self sample for nucleic acid extraction, bacteria, HPV and VOC analysis. Combinations of VOCs at selected concentration ratios may reflect the pathological status of HNSSC patients and hence therefore may serve as an additional tool for the diagnosis of HNSCC cancers. From this study and use of self collection kit, a risk factors flow chart is proposed for HPV (primary screening) and VOC analysis for diagnosis from the same saliva sample. The results of this study offer significant value using saliva of oral health and oral cancer disease risk evaluation.

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#0244

2 - Epidemiology and natural history

EPIDEMIOLOGY OF, AND RISK FACTORS FOR ORAL HUMAN PAPILLOMAVIRUS INFECTIONS AMONG SEXUALLY ACTIVE NIGERIAN FEMALES

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Background/Objectives: Oropharyngeal cancers are increasingly reported worldwide, and this has been associated with infection of oral human papillomavirus (HPV). The age standardized incidence rate of oropharyngeal cancers in women in Nigeria is 0.1/100,000 women/year compared to the global average of 0.5/100,00 women/year. There are no reported data on oral HPV infections among girls and women in Nigeria.To determine the prevalence of oral HPV infection and associated risk factors among females aged 18-45 years in Ibadan, Nigeria.

Methods: Randomly selected healthy sexually active females aged 18-45 years from two communities (peri-urban and urban) in Ibadan had face-to-face interviews and clinical examinations. An oral rinse and gargle sample was collected using Scopeâ mouthwash (Procter and Gamble) and stored at -80oC prior to HPV genotyping at the Catalan Institute of Oncology, Spain, by the Anyplexä II HPV28 assay. Logistic regression analysis was used to determine risk factors associated with prevalence of oral HPV infection.

Results: The results of 286 out of 310 females enrolled were analysed. The prevalence of any oral HPV infection was 46/286 (16.1%), any high-risk (HR) HPV was 30/286 (10.8%) and low-risk (LR) HPV was 27/286 (9.4%). Multiple oral HPV genotypes infections were detected among 13/286 (4.5%) of participants. The prevalence of any oral HPV infection decreased with age. Infection with multiple oral HPV infection rates increased with age. The commonest HR and LR HPV genotypes was HPV 51 (3.2%) and HPV 42 (3.8%), respectively. The adjusted odds of having any oral HPV infection were lower in those living in a peri-urban setting (aOR=0.37; 95%CI, 0.19-0.72) than those in urban settings, and higher odds of having oral HPV in those with concurrent cervical HPV infection (aOR=4.50; 95%CI 2.00-10.86) compared with those without cervical HPV. History of previous oral sex, mutual masturbation, smoking, alcohol use, illicit drug use, previous STIs, HIV status, concurrent vulvar and anal HPV infections were not associated with oral HPV infection.

Conclusions: The prevalence of oral HPV in Nigerian females was similar to the prevalence seen in high-income countries. Further longitudinal studies are needed to explore the incidence and clearance rates of oral HPV infections in sub-Saharan Africa.

References: NIL

MSS 04 - Vaccinating adult women and men – a new challenge for populations at risk

#1046

5 - HPV prophylactic vaccines

MID-ADULT VACCINATION IN WOMEN: REVIEW EVIDENCE FROM CLINICAL EFFICACY TRIALS

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Background/Objectives: The primary target age for prophylactic HPV vaccines is 9-12 years and before sexual debut. However, the potential for HPV infection and disease exists in women well into their 30's and 40's (either as reactivation of latent infection or new infections as a result of changes in sexual behaviour, [older age at first marriage, more lifetime partners and increase in divorce resulting in new partners later in life]): hence likely could benefit from prophylactic HPV vaccination.

Methods: The per protocol [PP or according to protocol ATP] and total vaccinated cohort [TVC or intention to treat ITT] efficacy results from Phase 3 clinical trials for the 2vHPV [Cervarix VIVIANE study with n of 5747 (1, 2) women > 25 years age] and 4vHPV in 25-45 years of age women [Gardasil trials FUTURE 111 with n 3819 (3, 4) were reviewed. For the 4vHPV trial, 3819 24-45-year-old women with no history of cervical disease or genital warts in the past 5 years were enrolled in a RCT to receive 4vHPV vaccine or placebo at day 1, months 2 and 6. The PP analysis was for those receiving three doses, naive to the relevant HPV types at day 1, and remained free of infection through month 7. A 6 years' post-vaccination follow-up of Columbian women [1335] from the original trial was made (5). For the 2vHPV trial, in a RCT women >25years (age stratified 26-35 years, 36-45 years, and ≥46 years) received 3 doses of vaccine with the primary endpoint being vaccine efficacy against 6-month persistent infection or CIN1+ associated with HPV 16/18 examining ATP (4407) and TVC (5747) for efficacy at 7 years follow up.

Results: At the end of study at 4 years, for the 4vHPV vaccine efficacy against the combined incidence of persistent infection, CIN/EGL related to HPV6/11/16/18 in the per protocol population was 88.7% whilst for the ITT populations it was 47.2%. At 6 years follow-up, no cases of HPV 6/11/16/18-related CIN or EGL in the PP population, immunogenicity against vaccine-related HPV types persisted, and no evidence of HPV type replacement. For the 2vHPV vaccine at month 84, in women seronegative for the corresponding HPV type in the ATP cohort for efficacy, vaccine efficacy against 6-month persistent infection or CIN1+ associated with HPV 16/18 was significant in all age groups combined at 90.5% and against HPV 16/18-related cytological abnormalities (ASCUS, LSIL and CIN1+ also significant). Significant cross-protective efficacy against 6-month persistent infection with HPV 31 and HPV 45. In the TVC, vaccine efficacy against CIN1+ irrespective of HPV was significant 22.9%.

Conclusions: 2vHPV and 4vHPV vaccines demonstrated high efficacy, immunogenicity, and acceptable safety in women aged 24-45 years, regardless of previous exposure to HPV vaccine type.

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#0342

2 - Epidemiology and natural history

The impact of HPV viral latency on vaccine effectiveness - evidence from modelling

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Background/Objectives: Mathematical models have been used to estimate the impact of human papillomavirus (HPV) vaccines on infection burden and cervical cancer. Models assume different mechanisms of naturally acquired immunity against re-infection, but processes of latency and reactivation of latent infection have not been explored.

Methods: This study uses an individual-based dynamic model to simulate randomised controlled trials (RCTs) for vaccine efficacy, using different assumptions about naturally acquired immunity and viral latency after clearance of HPV infection. Model estimates of vaccine effectiveness are compared to those from published RCTs. We then estimate the impact of the bivalent vaccine on HPV-16 and -18 infection burden in South Africa under these different assumptions.

Results: When assuming no latency, simulated vaccine effectiveness overestimates results from RCTs and the model cannot match the observed difference in vaccine effectiveness between total vaccinated cohorts and more HPV-naïve cohorts. The projected reduction in HPV-16 and -18 burden by 2045, following roll-out of pre-adolescent vaccination in 2014 and with hypothetical catch-up campaigns, does not depend on assumptions about natural immunity, but models that assume no latency predict greater reduction in HPV-16 and -18 burden than models that include reactivation of latent infection for all men and women.

Conclusions: Mathematical models that do not allow for reactivation of latent HPV infections may therefore overestimate the long-term impact of HPV vaccines.

CS 04 - HPV assays from practice to research development

#0506

8 - HPV testing

Clinical performance of HPV tests on alternative specimens.

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Background/Objectives: Since the introduction of HPV DNA detection in cervical cancer screening settings, interest for the use of alternative specimens has been increasing. Indeed, non or minimal invasive self-sampling and the option of at-home collection are considered to be important arguments to reach women not attending cervical screening programs. However, clinical validation of HPV detection assays on these alternative samples has been limited up to now.

Methods: A literature search was performed to identify relevant publications and reports on this topic.

Results: Large meta-analysis are available providing strong evidence on the performance of HPV assays on self-samples. However, it is important not to extrapolate these outcomes. Nice examples of studies showing the impact of applied assays, different sample formats, age of the participants as well as transport conditions were found.

Conclusions: To ensure correct conclusions on performance of HPV assays on alternative samples, the complete procedure starting from sample collection, to transport, specimen preparation and HPV detection should be validated. It is crucial that assay validation settings mimic real-world settings as much as possible.

MSS 05 A - Methylation : from molecular biology to clinical practice: Part A

#1055

17 - Methylation

Is the S5 DNA methylation test useful as a predictor of CIN3 and cancer in HPV-infected women?

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Background/Objectives: HPV DNA testing is becoming the preferred option for cervical cancer screening worldwide. The great strength of measuring HPV is unmatched sensitivity for cervical precancer, a weakness is that transient viral prevalence is high. HPV screening has problems with specificity and requires use of a triage test. A general characteristic of progressing epithelial precancers is increasingly diverse and large changes in DNA methylation. It is becoming quite interesting to determine if DNA methylation triage is ready for routine clinical use.

Methods: Review of published studies, systematic reviews and meta-analyses.

Results: The performance of the S5 DNA methylation test has been investigated in more than ten large studies including three randomized controlled trials, although the trials were not designed primarily to evaluate methylation triage. In all studies the performance of S5 was significantly better than the comparators which included triage by LBC cytology and/or HPV16/18 genotyping. Specificity of S5 was substantially higher than competing tests while sensitivity was as good or better than the comparators, ranging between 70-90% for CIN3 and 95-100% for invasive cancer. In three studies S5 or a component of the test was prognostic for CIN3 and invasive cancer up to five years in advance. Recently S5 was shown to give good results on self-collected vaginal cells.

Conclusions: The S5 DNA methylation test is highly reproducible and easy to use on exfoliated cells. The test shows excellent HPV triage performance providing rapid information for both diagnosis and prognosis.

References: Performance of DNA methylation assays for detection of high-grade cervical intraepithelial neoplasia (CIN2+): a systematic review and meta-analysis H Kelly, Y Benavente, MA Pavon, S De Sanjose, P Mayaud, AT Lorincz. British Journal of Cancer, 1-12. Virtues and weaknesses of DNA methylation as a test for cervical cancer prevention. AT Lorincz. Acta cytologica 60 (6), 501-512.

#0477

1 - Viral and molecular biology

EPIGENETICS IN HPV CAUSED CANCERS

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Background/Objectives: Cancer development following a persistent infection with high-risk human papillomavirus (hrHPV) is driven by additional genetic and epigenetic changes in the host-cell genome. Part of these host cell alterations are induced by expression of viral oncogenes E6 and E7 and include DNA methylation of tumor suppressor genes. Methylation of cytosines at CpG-sites in promoter regions can lead to gene silencing. The DNA methyltransferases (DNMTs) responsible for CpG methylation can be activated by both hrHPV E6 and E7. Accordingly, these molecular aberrations may already become apparent in HPV-induced precancerous lesions (e.g. high-grade cervical intraepithelial neoplasia; HGCIN) that are characterized by deregulated E6 and E7 expression. HPV-induced precancerous lesions represent a heterogeneous stage of disease, with varying duration of existence and cancer progression risks. We demonstrated that the level of molecular aberrations in HGCIN reflects the short-term progression risk to invasive cancer. Therefore, these aberrations may serve as molecular markers for the detection of HPV-induced precancerous lesions in need of treatment and cancer. Towards this goal we assessed the value of host cell DNA methylation markers to serve a triage markers in primary HPV screening and to enable the detection and risk assessment of HPV-induced precancerous lesions.

Methods: We performed genome wide DNA methylation profiling on cell lines, cervical tissues specimens and self-collected HPV-positive cervico-vaginal specimens (self-samples) to identify host cell genes that become methylated during HPV-induced carcinogenesis. Selected methylation markers were tested and validated in HPV-positive cervical scrapes and self-samples for HGCIN and cancer detection. The potential to detection anal cancer and precancerous lesions (HGAIN) was assessed in tissue specimens.

Results: We identified 8 methylation markers that are at least equal to cytology to detect HGCIN in hrHPV-positive cervical scrapes and have a similar good performance on hrHPV-positive self-samples. Importantly we demonstrated that these methylation markers detect virtually all cervical cancers and that a methylation test can be used to rule out cervical cancer. Interestingly, within HGCIN with varying cancer risks, distinct methylation patterns were seen. Our data indicate that so-called advanced lesions display a cancer-like methylation-high pattern and have a high short-term risk of progression to cancer. Similarly, we found that these methylation markers enable the detection of anal cancer can be used for cancer risk stratification of HGAIN.

Conclusions: In conclusion, methylation marker analysis provides an attractive triage tool for hrHPV-positive women, with the advantage of applicability to self-collected specimens allowing for full molecular cervical screening. Methylation markers lead to detection of advanced HPV-induced precancerous lesions in need of treatment and can prevent overtreatment of lesions with a low cancer risk.

#0493

7 - Immunotherapy - Immuno-oncology - New treatments

Therapeutic implications of demethylating drugs

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Background/Objectives: HPV-induced carcinogenesis is accompanied by epigenetic changes, specifically by alterations of DNA methylation patterns. Generally, methylation levels tend to increase during HPV-driven cancer development, both in the host cell as well as in the viral genome. Increasing evidence suggests that hypermethylation at distinct sites is not just a passive bystander effect but may have functional relevance for the carcinogenic process. In this context, we have previously demonstrated that hypermethylation in distinct CpG sites of the viral upstream regulatory region (URR) triggers uncontrolled expression of the HPV oncogenes E6 and E7 promoting carcinogenesis. HPV E6 and E7 themselves increase methylation levels in the cell allowing for hypermethylation of further genes, such as tumor suppressor genes, that may result in their transcriptional silencing. Considering the apparent functional relevance of hypermethylation for HPV-induced carcinogenesis we hypothesized that treatment with demethylating agents could represent a causal treatment approach for HPV-transformed lesions.

Methods: We treated a panel of HPV-transformed cell lines from the uterine cervix and the head and neck with different doses of the demethylating agent 5-aza-2'-deoxycytidine (DAC). DAC is a known DNA methyltransferase inhibitor (DNMTi) that is currently applied intravenously for distinct hematologic neoplasias such as the myelodysplastic syndrome. Treatment effects on methylation, proliferative activity and mechanisms of cell cycle arrest of treated cells were analyzed with multiple assays. To obtain data on demethylating treatment effects in a more realistic disease scenario we supplemented our analyses on monolayer cultures with analyses on three-dimensional tissue models.

Results: A dose- and time-dependent demethylation and significant down-regulation of proliferative activity were observed in all treated cell lines, both in monolayer as well as in three-dimensional tissue cultures. Inhibition of cellular proliferation was accompanied by the induction of cellular senescence and apoptosis.

Conclusions: Treatment with demethylating agents represents a targeted therapeutic approach for HPV-induced lesions by reversing the malignant phenotype of HPV-transformed cells.

CS 05 - Age to start and to stop screening and how it will change with HPV

#0388

34 - Economics and modelling

WHEN TO START AND STOP SCREENING WITH PAP AND HPV: MODELS FOR POLICY DECISION MAKING

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Background/Objectives: Decision models are increasingly used to aid decision-making and in screening guidelines because they can link intermediate endpoints from trials with long-term clinical outcomes. Due to long-term preventive effects of screening, the impact of screening at each age is often difficult to disentangle in empirical studies. We examine how modeling evidence can be used to supplement empirical evidence in the context of deciding at which ages to start and stop screening.

Methods: A Markov model calibrated to Canadian epidemiological data is used to illustrate the impact of screening at different ages and calculate lifetime risks of cervical cancer in screen-negative women. The impact of model assumptions affecting results will be reviewed.

Results: Our model predicts that increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. A 70-year old woman had an average remaining lifetime risk of 1 in 588 (95% prediction interval 451-873) if she stopped screening. Her remaining lifetime risk at age 70 years was reduced to 1 in 1206 (942-1,748) if she had a negative exit cytology test, 1 in 6,525 (3,167-18,664) if she had a negative exit HPV test, and 1 in 9,550 (4,928-23,228) if she had a negative exit co-test for cytology and HPV. Predicted life years gained and quality-adjusted life years (QALY) gained from continuing screening diminished after age 65, suggesting more harms than benefits of screening past this age. Starting screening with HPV testing from age 20 was predicted to lead to substantial harms for very little benefit due to a high number of expected colposcopy referrals, however screening from age 25 onwards was predicted to start leading to life year gains and QALY gains from prevented cancers. The key model assumptions influencing predictions were 1) whether the HPV infections and cervical cancer lesions have the same risk of oncogenic progression at younger and older ages than in women 30-65, and 2) the impact of being screen-postive on women's quality of life (the value attributed to screening harms).

Conclusions: The optimal ages to start and stop screening depend on societies' and individuals' risk tolerance, how they value harms and benefits of screening, and available resources. Nonetheless, our model results suggest that benefits of screening are likely to outweigh its harms between ages 25-65, supporting recommendations to screen at these ages.

#0629

14 - Screening methods

WHEN TO START AND STOP SCREENING WITH HPV TESTING: THE IMPORTANCE OF THE KNOWLEDGE ON THE NATURAL HISTORY OF THE DISEASE

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Background/Objectives: In order to evaluate if earlier age to stop was possible with HPV-based screening we computed the risk of high-grade CIN and invasive cervical cancer (ICC) below and above age 50 in the two arms of the 4 European randomized controlled trials and used a mathematical model in order to interpret results.

Methods: We used data of the NTCC, POBASCAM, ARTISTIC and Swedscreen RCTs to compute the incidence of CIN2/3 and of ICC after a negative entry cytology in the control arm and 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). To evaluate how much systematically very low sensitivity of cytology for a subset of precancerous lesions and cohort effects could explain results, we predicted by the model the difference between women aged 50-64 and 25-49 years in risk of CIN2/3 and of ICC 3 years after normal cytology, under different scenarios concerning precancerous lesions poorly detectable (sensitivity 5%) by cytology and year of start of screening.

Results: The age-adjusted relative incidence in the experimental vs. conventional 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 arm-age interaction was not significant (p=0.14 for CIN2/3 and 0.21 for ICC). The 3.5-year risk of ICC per 10,000 women aged < and ≥50 years were 1.2 and 2.5 respectively after a negative entry cytology and 0.3 and 1.0 respectively after a negative HPV test. Model scenarios assuming low sensitivity of cytology for some lesions predicted ICC risk to increase above age 50 as more as their frequency increased while an opposite age trend was predicted in their absence unless in scenarios with extremely recent start of screening. The ICC risk increase at age ≥50 was mediated by an accumulation of lesions undetected from long time (>20 years). Only very few sets of parameters could fit the age distribution of ICC incidence in NTCC centers without assuming difficult-to-detect pre-cancers.

Conclusions: The effect of HPV was similar in both age groups. However, at variance with CIN2/3, the risk of ICC increased at age ≥50 in both arms. Model simulations suggest that the presence of pre-cancers systematically difficult to detect by cytology could represent an explanation. Study women were at their first screen with HPV and lesion accumulation at older age had already occurred. Thus, ICC risk after negative HPV increasing at age ≥50 is plausibly transient.

#0233

9 - HPV screening

AGE TO START AND TO STOP SCREENING AND HOW IT WILL CHANGE WITH HPV

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Background/Objectives: Background: In non-HPV-vaccinated, non-screened women, the incidence of cervical cancer increases sharply from age 20 to age 45 and decreases thereafter indicating start of screening at age 30 and stop at about age 60. However, many countries have chosen to start screening earlier. In a non-HPV-vaccinated, well-screened women, the overall incidence is considerably lower but with two peaks at about age 45 and at about age 75. Over time, the second peak has moved towards older age indicating that it represents residual disease from less-screened generations. Women HPV-vaccinated as girls are now reaching screening age, and it is a new challenge is to optimize screening for these women.

Methods: Methods: In Denmark, 3-yearly cytology-screening starts at age 23, becomes 5-years from age 50, and ends with an HPV-exit test at age 60-64. For half of women aged 30-59, HPV-screening will replace cytology in 2020. To take account of the second incidence peak, all women aged 69+ were offered HPV-screening in 2017. For women born in 1994 and offered HPV-vaccination at age 14, a trial is ongoing with HPV-testing in addition to the routine cytology. The purpose being to assess safety of 6-yearly primary HPV-screening.

Results: Results: In Denmark, incidence of cervical cancer decreased from 40 to 10 per 100,000, but no change has been seen during the last 15 years, despite population-based screening. HPV-screening of elderly women showed decreasing HPV-prevalence by increasing age with no reflection of the second peak in cervical cancer incidence. Supplementary HPV-testing of women born 1994 showed very low levels of HPV 16 and 18, but an increase in prevalence of other HPV-types from 27% for non-vaccinated to 35%.

Conclusions: Conclusion: Cytology screening has been a successful tool in control of cervical cancer, but is seems to have reached its potential. The second peak in cervical cancer in elderly women is not reflected in an increased HPV-prevalence, indicating that it does not reflect new infections. HPV 16 and 18 have been well controlled by HPV-vaccination, but the possible impact of an increasing prevalence of other HPV-types needs to be investigated.

MSS 05 B - Methylation : from molecular biology to clinical practice: Part B

#0550

17 - Methylation

PERFORMANCE OF A COCKTAIL HPV DNA METHYLATION TEST WITH 12 OR MORE TYPES

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Background/Objectives: Human papillomavirus (HPV) testing is the most sensitive method for cervical screening, but its use is limited by lack of specificity, and triage tests are required to distinguish benign HPV infections from precancers. Previous studies have shown that HPV DNA methylation testing is a promising triage option for women testing HPV-positive; however, these findings were restricted to only a few HPV types (HPV16, 18, 31, 33, and 45). Here, we evaluated the performance of methylation testing for all 12 high-risk HPV genotypes for triage of HPV-positive women.

Methods: In this nested case-control study, we tested up to 30 cases with cervical intraepithelial neoplasia grade 3 (CIN3) or adenocarcinoma in situ (AIS) and 30 normal controls (<CIN2) positive for each carcinogenic type (single infections with 16/18/31/33/35/39/45/51/52/56/58/59). HPV methylation in viral L1 and L2 genes (about 9 CpGs per type) was measured using next-generation bisulfite sequencing. We calculated odds ratios (OR) using logistic regression for the association of HPV methylation with precancer and assessed the discrimination between cases and controls using areas under the curve (AUC). Using a fixed sensitivity of 80%, we evaluated the specificity, Youden's Index, and the risk of CIN3/AIS for the best performing CpG sites for each type, and compared the performance of an explorative multi-type methylation assay with current triage strategies.

Results: We observed significant associations of higher HPV DNA methylation with CIN3/AIS across all 12 types (OR range 4-28.0). AUCs for the top CpG sites ranged from 0.71 (HPV51 and HPV56) to 0.86 (HPV18). A combined 12-type methylation assay had the highest Youden index (0.46), compared with cytology (0.31) and a 5-type methylation assay, including only previously described types (0.26). The 12-type methylation assay had higher sensitivity (80% vs. 76.6%) and lower test positivity compared with cytology (38.5% vs. 48.7%). The risk of CIN3/AIS was highest for methylation positives compared to other triage strategies, and was clearly above a colposcopy referral threshold.

Conclusions: We observed a strong association of increased HPV methylation with precancers across 12 HPV types, suggesting that methylation is a general phenomenon in the transition from HPV infection to precancer. For most types, clinical performance of HPV methylation was comparable to or exceeded that of cytology. Development of a combined multitype methylation assay may serve as a triage test for HPV-positive women.

#0752

17 - Methylation

Routine DNA methylation testing in Colombia, is it feasible?

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Background/Objectives: Screening with hrHPV test followed by cytology of hrHPV+ women were approved in Colombia in 20141, however, conventional cytology remains the only test widely available in the health care system. Inappropriate follow-up is the main limitation for the effectiveness of screening for cervical cancer in Colombia2. A full molecular screening and triage follow-up may help to overcome this limitation. The molecular S5 DNA methylation test3,4, a new alternative to cytology and HPV16/18 genotyping to triage high- risk HPV positive (hrHPV+) women, has not been validated in Low-Middle-Income countries. We compared the performance of S5 to HPV16/18 genotyping and conventional Pap smear to detect CIN3+ and CIN2+ in hrHPV+ women selected from a randomized pragmatic trial that followed-up for 24 months, 2661 Colombian women with an earlier borderline abnormal cytology.

Methods: We included all hrHPV+ cases of CIN2 (n=139) and CIN3+ (n=44) found in our trial (n=183) and 183 age- and period of diagnosis-matched, hrHPV+ controls with less than CIN2 (<CIN2). Histological diagnosis was reviewed by expert panel and baseline hrHPV+ specimens were HPV genotyped and tested for the S5 classifier, blinded to cytology, histology and initial HPV test results. The established S5 cut-off as well as other selected cut-off values were examined to define methylation positives. Differences in sensitivities and specificities of S5 and the other tests were examined by McNemar's test with continuity correction.

Results: At a 3.1 cut-off, sensitivity of S5 (64·58%, 95% CI 51·05-78·11) for CIN3+ was higher than the sensitivity of HPV16/18 (50%, 95% CI 35·86-64·14, p=0·0233) and cytology (36·96%, 95% CI 23·30-50·61, p=0·0088) and the specificity (64·15%, 95% CI 58·88-69·42) was similar to HPV 16/18 (61·01%, 95% CI 55·65-66·37) but lower than cytology (73·60%. 95% CI 68·75-78·44). The sensitivity of S5 at cut-off 3.1 for CIN2+ (55·19%, 95% CI 47·99-62·40), was also higher than the sensitivity of HPV16/18 (48·09%, 95% CI 40·85-55·33, p=0·0164) and cytology (29·51%, 95% CI 22·90-36·12, p <0·0001) and the specificity (75·96%, 95% CI 69·76-82·15) was similar to the specificity of cytology (76·50%, 95% CI 70·36-82·65, p=1) and higher than of HPV16/18 (67·21%, 95% CI 60·41-74·01, p=0.0062). The combination of HPV16/18 plus cytology did not exceed the sensitivity of S5 at 3.1 cut-off for CIN2+ or CIN3+ and the specificity was significantly lower.

Conclusions: High sensitivity is crucial in LMICs. In this pragmatic trial we demonstrated that S5 at a cut-off 3.1 exceeded the sensitivity of HPV16/18 genotyping and cytology and had a comparable specificity to detect CIN2+ and CIN3+ in hrHPV-positive Colombian women with earlier borderline cytology. Furthermore, S5 triage had comparable sensitivity to a combination of cytology and HPV16/18 genotyping but S5 test had fewer false positives.

References: 1. Colombian Ministry of Health (Ministerio de Salud y Protección Social). [Clinical Practice Guide (CPG) for the detection and management of precancerous cervical lesions]. In: Colombian Ministry of Health editor. Guia No GPC 2014-44. Bogota, Colombia: Colombian Ministry of Health; 2014. p. 318. 2. Murillo R, Almonte M, Pereira A, et al. Cervical Cancer Screening Programs in Latin America and the Caribbean: Prevention of Cervical Cancer in Latin America and the Caribbean Region: Progress and Challenges on HPV Vaccination and Screening. Vaccine 2008; 26(Supplement 11): L37-L48. 3. Cook DA, Krajden M, Brentnall AR, et al. Evaluation of a validated methylation triage signature for human papillomavirus positive women in the HPV FOCAL cervical cancer screening trial. Int J Cancer 2019; 144(10): 2587-95. 4. Lorincz AT, Brentnall AR, Scibior-Bentkowska D, et al. Validation of a DNA methylation HPV triage classifier in a screening sample. Int J Cancer 2016; 138(11): 2745-51.

#0318

14 - Screening methods

Performance of the GynTect methylation assay in triage of HPV positive women

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Background/Objectives: A change of the current screening algorithms to a HPV-based screening setting is being implemented in several countries due to the higher sensitivity of HPV testing compared to cytology. Reliable triage methods are, however, essential in such a setting to avoid overtreatment and higher screening costs. Specific DNA methylation patterns may provide a suitable tool especially with regard to keeping false positive rates low.

Methods: GynTect® is a methylation assay using six human DNA methylation sites, which gives a score as output result. The more marker (weighted) that are positive, the higher is the final score.

Results: Several retrospective studies show a 100% sensitivity for cancer cases, irrespective of sample type (liquid based cytology scrapes, STM scrapes, tissue samples, self samples). Detection rates of CIN lesions are increasing with the severity of the lesion, namely 18.9% CIN1 (n=37), 32.1% CIN2 (n=53) and 62.0% CIN3 (n=236). Looking at samples from routine screening with NILM cytology (Pap 1, n=733), only 3.4% showed positive GynTect® results. Noteworthy is also the overall score of the GynTect® result. The more severe the lesion, the higher is the GynTect® score suggesting that the score may also be an indicator for the progression potential of a lesion.

Conclusions: DNA methylation analysis of the GynTect® test in cervical scrapes consistently detects cervical cancer and the majority of CIN3 as well as a subset of CIN1/2 lesions, whereas the detection rate among cytology-normal samples is extraordinarily low. Furthermore, data suggest that this methylation panel has prognostic potential and GynTect® negative women, even with prevalent high grade CIN, are at very low risk to develop a malignant lesion. A multicentre prospective observational study (GynTect-Pro) addressing the prognostic value of the marker panel is ongoing. Altogether, the GynTect® assay based on detection of six methylation markers may provide an excellent tool for triage within cervical cancer screening.

#0403

12 - Molecular markers

HPV triage - longitudinal studies on host DNA methylation

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Background/Objectives: DNA methylation analysis of HPV-positive cervical scrapes using host cell genes FAM19A4 and mir124-2 has shown a good cross-sectional clinical performance. In our recent studies, we assessed the longitudinal outcome of FAM19A4/mir124-2 methylation analysis in HPV-positive screening cohorts with 14 years of follow-up.

Methods: DNA isolated from baseline HPV-positive cervical scrapes of women aged 30-60 years from two large population-based screening cohorts (POBASCAM n=1,025 and VUSA-screen n=979) was subjected to bisulphite treatment and subsequent DNA methylation analysis for FAM19A4 and miR124-2 genes (QIAsure Methylation Test). Histo- and cytopathology follow-up data were collected through the nationwide network and registry of histopathology and cytopathology (PALGA).

Results: Kaplan-Meier estimate of 14-year cumulative cervical cancer incidence in POBASCAM cohort was 1.7% (95% CI: 0.66-3.0) among baseline methylation-negative and 2.4% (95% CI: 1.4-3.6) among baseline cytology-negative women (risk difference: 0.71% [95% CI: 0.16-1.4]). Kaplan-Meier estimates of 14-year cumulative CIN3+ incidence of HPV positive women with a negative methylation and a negative cytology triage test were comparable (16.3% and 15.6%, respectively). Similar findings were observed in VUSA-screen cohort.

Conclusions: FAM19A4/miR124-2 methylation analysis has a good triage performance on baseline HPV-positive screening samples, equalling long-term negative predictive value of cytology triage testing. A negative FAM19A4/mir124-2 methylation test provides a low cervical cancer risk in HPV-positive women of 30 years and older. Therefore, FAM19A4/miR124-2 methylation analysis is a promising alternative to cytology in triage scenarios in HPV-based cervical screening.

MSS 07 - Artificial intelligence-digital pathology and machine learning applications for precision prevention of cervical cancer

#1067

21 - Artificial Intelligence

Artificial Intelligence in Breast Imaging

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Background/Objectives: To present history of CAD experiences in Breast Imaging To define main differences with traditional CAD and new tools of Artificial Intelligence in Breast Imaging To show results of main AI results in Mammography To show other AI experiences in other Breast Imaging techniques

Methods: History and main results of traditional CAD studies, performed around 2000's will be presented. Main differences with new artificial Intelligence algorithms will be described. Main commercially AI algorithms evaluated in Mammography will be presented. Opening through Data challenge experiences and other experiences in Breast imaging will be provided.

Results: First CAD experiences in Mammography were published at the beginning of 2000's. Main objectives of CAD in mammography were focused on breast cancer detection. First results were promising showing high detection rates, and cancer not seen without CAD. A reimbursement rate for CAD detection was applied in the States, and CAD software were largely used until 2016. Nevertheless, these results published on retrospective studies and small cohorts were not confirmed in large prospective screeening trials, with many false positive results. Recently, new AI algorithms based on machine and deep learning seems to be more promising, allowing cancer detection and characterization, with low false positive rates. Other AI algorithms may focus on other key questions in breast imaging : risk assessment, quality evaluation, ultrasound and MR detection. These last 2 years, 2 big successful datachallenges were organized during the French Congress of Radiology to adress the impact of AI in clinical questions ; beside them, one concerned the evaluation of AI ilesion characterization on Breast MRI.

Conclusions: AI algorithms based on deep learning techniques are a more and more concern focus in Radiology. One common question in Breast Imaging is not only breast cancer detection but also lesion characterization. Artificial Intelligence may help radiologists to improve their skills, while saving time allowing them to be more focused on difficult cases and patient care. One important point underlined these last 2 years, is the input of AI with the radiologists and not against or without radiologists.

SS 10 - Cervical screening of vaccinated birth cohorts

#0387

38 - Public health

DESIGN AND IMPLEMENTATION OF SCREENING PROGRAMS FOR VACCINATED COHORTS

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Background/Objectives: Declines in the prevalence of oncogenic HPV infections will inevitably lead to a reduced positive predictive value (PPV) of cervical cancer screening in vaccine-eligible cohorts. An important dilemma facing policy makers is whether screening strategies should be personalized to a woman's vaccination status, or whether a developping an uniform strategy for vaccine-eligible cohorts is more appropriate.

Methods: We review the challenges of personalized screening and why a uniform strategy by cohort is likely the most feasible using the Canadian context as an example.

Results: Healthcare delivery is decentralized in Canada, with screening registries and immunization records siloed by province and of varying quality. Girls' HPV vaccination coverage varies substantially by province, mostly ranging from 60-90%. Interprovincial migration is high, with 15% of Canadians living in a province other than their birth province, mostly from migration in young adulthood to pursue educational and economic opportunities. Furthermore, 22% of Canadians are foreign-born, with most immigrating between the ages of 20-50. This creates substantial difficuly in linking screening registry data with vaccination records. Personalized screening recommendations are likely unfeasible as many screen-eligible women will have no immunization records. In any case, mathematical modeling suggests substantial vaccine herd effects to unvaccinated women in vaccine-eligible cohorts, with the prevalence of HPV infection likely to also decline in the unvaccinated women. Current Canadian Task Force on Preventive Health Care screening recommendations which date from 2013 do not provide any guidance for screening in vaccinated cohorts and still do not recommend use of HPV tests for screening. However, many provinces have recently increased their age to start screening from 21 to 25, in part due to a lack of evidence of screening effectivness at this age, but also likely due to evidence that the incidence of dysplasia has decreased in young women from vaccine-eligible cohorts. It is therefore likely that future updates in screening guidelines will be cohort-based and will respond to changes in screening outcomes rather than vaccination coverage.

Conclusions: Screening registries will be vital to determine whether screening programs are performing well in vaccine-eligible cohorts and to justify changes in recommendations for vaccinated cohorts, including key quality indicators such as HSIL detection rates per 1,000 screened, cytology-histology agreement, and screening history in cervical cancer cases.

CS 08 - Management / Colposcopy

#1042

12 - Molecular markers

CAN WE MAKE PATHOLOGICAL DIAGNOSIS LESS SUBJECTIVE AND VARIABLE?

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Background/Objectives: Biopsy diagnosis is a key stage in deciding the management of women with abnormal cytology who are hrHPV positive in all cervical screening systems. Women whose biopsies are graded HSIL/CIN2+ are mostly treated, usually by LEEP. This may result in overtreatment of regressing lesions, as 50% of CIN2 (and some CIN3) is thought to regress if left untreated, and is not without risk to the reproductive health of young women. More accurate prediction of progressing high-grade lesions is important. To achieve this it is first necessary to have standardised, reliable classification and diagnostic process for HSIL lesions and then to identify the relation of this classification to their behaviour. The immunohistochemical biomarker p16 has been in use for almost 20 years as a surrogate marker of hrHPV E7 transforming gene activity, and its interpretation shown to be very reproducible. Its current value in biopsy diagnosis is very limited according to the current LAST guidelines. Combination of p16 with Ki67 and scoring of both these immunohistochemical biomarkers can produce a reliable and accurate predictor of CIN3. The heterogeneity of CIN2 and the limitation of p16 as a single marker of transformation by hrHPV are shown by the use of scoring of combined biomarkers p16 and HPV E4. The scoring of staining by combination biomarkers could provide a reproducible standard for classification and sub-classification of HSIL by cervical biopsy. This could be used to standardise comparisons between centres and studies. It can be related to other biomarkers of precancerous progression and is being investigated for its ability to predict the outcome of untreated CIN2 lesions.

Methods: xxx

Results: xxx

Conclusions: xxx

#1061

23 - Colposcopy

MANAGEMENT OF CERVICAL ABNORMALITIES IN PREGNANCY

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Background/Objectives: Approximately 1-3 % of women diagnosed with cervical cancer are pregnant or post- partum at the time of diagnosis. The peak incidence of HSIL is between 25-35 years old in the same decade in which most pregnancies occur. The natural history of HSIL does not seem to be influenced by the pregnancy itself.

Methods: The primary goal of colposcopy in pregnancy is to eliminate cervical cancer. There are a lot of pitfalls associated with the evaluation of cervical abnormalities in pregnancy: glandular hyperplasia, immature metaplasia, mis-interpretation of cytology, increased caliber of vessels and decidual reaction.

Results: There are also some difficulties attached to the technic in relation with the pregnant state such as cervical hyperemia, obscuring mucus, bleeding on cervical contact, prolapsed vaginal walls and bleeding after cervical biopsy. The indications of colposcopy are mainly abnormal cervical cytology or cervical lesions suspicious of invasive cancer. Moreover, if a patient is followed by colposcopy after treatment for HSIL, repeat colposcopy should not be delayed because of pregnancy. The patient must be seen in colposcopy with the same recommendation as non-pregnant patients. Cytology with ASCUS and HPV-HR (+), LSIL, ASCH, HSIL, and AGC must be evaluated by colposcopy. Biopsy should be performed if suspicion of an invasive lesion. If the colposcopy corroborates HSIL without suspicious invasive lesion, biopsy is not required. The patient will be followed by colposcopy at 12-20 weeks intervals.

Conclusions: During pregnancy, treatment of lesions is postponed after delivery. We rarely performed LEEP or cold knife excision during pregnancy. These procedures are associated with possible significant complications such as important bleeding or miscarriage. If cancer is diagnosed during pregnancy, surgical procedure can be offered according to the stage of the disease under care of the gynecologist-oncologist.

References: None

MSS 08 - Challenges for HPV self-sampling as primary screening tool in organized cervical screening

#0401

10 - Self-sampling

Challenges for triage

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Background/Objectives: HPV testing with a clinically validated PCR-based assay has shown similar accuracy on self-collected and clinician-collected samples in terms of the detection of CIN2+ or CIN3+ lesions (IMPROVE study). These findings support the use of HPV self-sampling as a primary screening method in routine screening. A distinct triage test is needed for women with a positive HPV test result as most infections are transient and only a subset of HPV-positive women harbors clinically relevant disease in need of treatment. Given that cytology, as yet, cannot reliably be performed on self-collected screening samples, triage of women with an HPV-positive self-sample by cytology requires an additional visit at a clinic for taking a Pap smear. This may result in significant loss to follow-up. The challenges for triage are discussed as well as potential molecular triage tests feasible on self-samples. Molecular triage markers such as DNA methylation markers are particularly promising, as they can be objectively tested directly on HPV-positive self-samples.

Methods:

Results:

Conclusions:

References: Polman NJ, Ebisch RMF, Heideman DAM, Melchers WJG, Bekkers RLM, Molijn AC, Meijer CJLM, Quint WGV, Snijders PJF, Massuger LFAG, van Kemenade FJ, Berkhof J. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. Lancet Oncol. 2019 Feb;20(2):229-238. doi: 10.1016/S1470-2045(18)30763-0. Epub 2019 Jan 15. PubMed PMID: 30658933.

SS 11 - Control of high-risk HPV transmission in clinical practice

#1064

8 - HPV testing

HEALTH-CARE ASSOCIATED TRANSMISSION OF INFECTIOUS AGENTS

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Background/Objectives: Hospital-acquired pathogens are spread by hands of staff and patient and by contact with the environment. Endoscopes and ultrasound probes may transmit bacteria or viruses if inadequately decontaminated, for example via the handpiece. Production of aerosols can also transmit bacteria or virus.

Methods: Published studies of vaginal ultrasound probe decontamination were reviewed.

Results: Ultrasound probes are contaminated by handling and by perforation of protective sheath. Standard disinfectants providing low level disinfection are inadequate to eradicate Human Papilloma Virus DNA. Isolation, hand hygiene and cleaning are the three critical infection prevention measures. Automation has improved reproducibility but turnaround must be rapid for ultrasound probes. Disinfectant wipes, hydrogen peroxide mist and UV-C disinfection can all deliver rapid high level disinfection and are effective in eliminating Human Papilloma Virus but require initial manual cleaning.

Conclusions: Measuring efficacy against Human Papilloma Virus is not standardized and comparative studies between the methods are needed.

References: Manson LT1, Damrose EJ. Does exposure to laser plume place the surgeon at high risk for acquiring clinical human papillomavirus infection? Laryngoscope. 2013 Jun;123(6):1319-20. doi: 10.1002/lary.23642. Kola A1, Piening B1, Pape UF2, Veltzke-Schlieker W2, Kaase M3, Geffers C1, Wiedenmann B2, Gastmeier P1.An outbreak of carbapenem-resistant OXA-48 - producing Klebsiella pneumonia associated to duodenoscopy. Antimicrob Resist Infect Control. 2015 Mar 25;4:8. doi: 10.1186/s13756-015-0049-4. eCollection 2015. Koo VS1, O'Neill P, Elves A. Multidrug-resistant NDM-1 Klebsiella outbreak and infection control in endoscopic urology. BJU Int. 2012 Dec;110(11 Pt C):E922-6. doi: 10.1111/j.1464-410X.2012.11556.x. Epub 2012 Oct 26. M'Zali F1, Bounizra C1, Leroy S2, Mekki Y3, Quentin-Noury C1, Kann M1. Persistence of microbial contamination on transvaginal ultrasound probes despite low-level disinfection procedure. PLoS One. 2014 Apr 2;9(4):e93368. doi: 10.1371/journal.pone.0093368. eCollection 2014. Levin PD1, Golovanevski M, Moses AE, Sprung CL, Benenson S.Improved ICU design reduces acquisition of antibiotic-resistant bacteria: a quasi-experimental observational study. Crit Care. 2011;15(5):R211. doi: 10.1186/cc10446. Epub 2011 Sep 14. Ma ST1, Yeung AC, Chan PK, Graham CA.Transvaginal ultrasound probe contamination by the human papillomavirus in the emergency department. Emerg Med J. 2013 Jun;30(6):472-5. doi: 10.1136/emermed-2012-201407. Epub 2012 Jul 3. Johnson S1, Proctor M, Bluth E, Smetherman D, Baumgarten K, Troxclair L, Bienvenu M. Evaluation of a hydrogen peroxide-based system for high-level disinfection of vaginal ultrasound probes. J Ultrasound Med. 2013 Oct;32(10):1799-804. doi: 10.7863/ultra.32.10.1799. Kac G1, Podglajen I, Si-Mohamed A, Rodi A, Grataloup C, Meyer G.Evaluation of ultraviolet C for disinfection of endocavitary ultrasound transducers persistently contaminated despite probe covers. Infect Control Hosp Epidemiol. 2010 Feb;31(2):165-70. d

#1069

20 - New technologies

ASSESSING THE EFFICACY OF HUMAN PAPILLOMAVIRUS DISINFECTION AND THE RISK OF TRANSMISSION FROM CLINICAL LESIONS

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Background/Objectives: Studies have found that nuclease resistant HPV genomes can be detected on transvaginal ultrasound probes following proper hospital disinfectant procedures (1-3). Recent reports have concluded that oncogenic HPVs derived from laboratory tissue-based models are not susceptible to certain high-level disinfection protocols (4-6), further intensifying the concern that medical instruments may provide transmission of nosocomial HPVs infections. Therefore, we aimed to determine the infectious load of HPVs from clinical lesions and to investigate the effectiveness of classical disinfection protocols on HPV virions derived from model systems.

Methods: Infectious HPV virions were isolated from the 293T transfection system, organotypic epithelial tissue cultures, and mouse xenografts. Clinical samples from recurrent respiratory papillomas (RRPs) and anogenital warts were obtained under IRB approval using emery paper to swab apical wart surfaces. The infectivity of HPV virion stocks was measured by detection of spliced viral E1^E4 mRNAs in infected HaCaT keratinocytes. Infections were validated by time dependent detection of E1^E4 mRNAs, resistance of viral stocks to ribonuclease and susceptibility of virus stocks to antibody-mediated neutralization. We established that our infectivity assay demonstrated a dynamic range of >5 log10 detection of E1^E4 mRNAs, which is important in determining the level of disinfection achieved. Suspension-based disinfection protocols employed ortho-phthalaldehyde (OPA) and hypochlorite.

Results: In contrast to prior reports, we found that validated HPV virions obtained from a variety of sources were susceptible to a 2.5 to 4 log10 reduction in infectious titer when exposed as directed to OPA or hypochlorite. Some HPV virion stocks failed to meet the infectivity criteria of time dependent detection of E1^E4 mRNAs, resistance to ribonuclease and susceptibility to antibody-mediated neutralization. Such unvalidated virus stocks are likely to produce spurious results and lead to confounding conclusions. Preliminary assessment of HPV infectious titers from clinical lesions suggest that compared to common warts, clinical RRP and anogenital warts have low levels of virions present at apical surfaces.

Conclusions: We conclude that HPVs are susceptible to disinfection by OPA and hypochlorite. Studies are underway to carefully assess the infectious titers of virions present HPV-induced lesions to better determine the risk of transmission from HPV-induced warts at mucosal surfaces.

References: 1. Casalegno et al. PLoS One. 2012; 7(10):e48137. 2. Ma et al. Emerg. Med. J. 2013; 30(6):472. 3. M'Zali et al. PLoS One. 2014; 9(4): e93368. 4. Meyers et al. PLoS One. 2017;12(10):e0187377. 5. Meyers et al. J Antimicrob Chemother. 2014;69(6):1546. 6. Ryndock et al. J Med Virol. 2016;88(6):1076.

CS 09 - Treatment of anal cancer precursors

#0253

27 - Anal neoplasia

Novel approaches of detection of anal lesions

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Background/Objectives: High-grade anal intraepithelial neoplasia (HGAIN; AIN2/3) are highly prevalent in HIV+ men, but only a minority will progress towards cancer. Currently, risk of progression cannot be established, and therefore all HGAIN are treated, resulting in overtreatment. In this study we validated previously identified host cell DNA methylation markers for the detection of HGAIN and anal cancer in a large independent sample series, and assessed their association with progression to cancer.

Methods: A cross-sectional series of 345 anal cancer, AIN3, AIN2, AIN1 and control tissue specimens of HIV+ men was tested for DNA methylation of six genes using quantitative methylation-specific-PCR. We determined accuracy for detection of AIN3 and cancer (AIN3+) by simple and multiple logistic regression, followed by leave-one-out-cross-validation. In a unique longitudinal series of cases with biopsies of both anal cancer and preceding HGAIN at the same localization, we compared methylation levels to the cross-sectional series.

Results: Methylation of all genes increased with increasing severity of disease ($p<0.05$). HGAIN revealed a heterogeneous methylation pattern, with a subset resembling cancer. The gene ZNF582 showed highest accuracy (AUC=0.88) for AIN3+ detection, which was slightly improved by addition of ASCL1 and SST (AUC=0.89). In the longitudinal series, HGAIN preceding cancer displayed high methylation levels, similar to cancers.

Conclusions: We validated methylation markers for the detection of anal cancer and HGAIN; high methylation levels in HGAIN were associated with progression to cancer. Therefore, these markers provide a promising tool to identify HGAIN in need of treatment, preventing overtreatment of HGAIN with a low cancer risk.

MSS 09 - Cervical screening programs from a flow-chart point of view

#0618

9 - HPV screening

"Cervical screening programs from a flow-chart point of view" The Scottish perspective

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Background/Objectives: Scotland has had an organised cervical screening programme since 1988, with full computerisation achieved in 1990. Initially, there were a variety of systems in use but since 2007 there has been a single system - Scottish Cervical Call-Recall system (SCCRS). This contains a complete screening history for all women, including legacy data from systems in use since 1990. Well-developed QA structures and clinical protocols underpin the Scottish programme, subject to regular review and monitoring. The protocols and standards are published in SCSP documentation, but for day-to-day usage they reside in the brains of clinicians, clerical and laboratory personnel. Reliance on automation and computing is limited to calling women at the prescribed time and to referral for colposcopy following a screening test. However, with the introduction of HPV primary screening in 2020, the opportunity has been taken to take advantage of the simplicity and automation of the HPV result to extend the role for automated call and recall. This has necessitated the formalisation of the clinical management protocols so that they can be coded into SCCRS.

Methods: The clinical pathways, the rationale for them and the computing consequences of them will be presented and discussed.

Results: n/a

Conclusions: n/a

SS 12 - Therapeutic options for low-risk HPV infection and disease

#0755

7 - Immunotherapy - Immuno-oncology - New treatments

Overview of therapeutic drugs for benign and neoplastic HPV lesions

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Background/Objectives: The vast number of HPV-associated dysplasias and cancers that will arise in the next 20 years in people who did not accept the HPV vaccines or who did not have access will require therapeutic responses. HPV lesions may be self-recognized while other HPV infections will be identified by population-based screening. Two distinct stages of diseases are well known: those in which the HPV genome is episomal and autonomously replicating, and those in which the viral genome is integrated into host chromosomes, where persistence and risk are linked to the replicative potential of the cell. Early screening and immediate antiviral treatment together provide the ideal medical and public health strategy for HPV management because the potential for sexual transmission will have been averted and the possibility of subsequent neoplastic progression reduced. For centuries, most of the available topical therapies were based on "folk medicine" involving natural products derived from plants while more recent HPV inhibitors have some degree of chemical modification as well as formulations customized to different anatomic sites. These include salicylic acid (from willow tree bark), podophylotoxin (American May apple) and derivative topoisomerase II inhibitors (Etoposide), sinecatechins (green tea extract) and various essential oils as excipients. Treatments for recurrent respiratory papillomatosis include indole-3-carbinol (cruciferous vegetables), artemisinin (worm wood and retinoids (carrots). Pharmaco-chemistry has provided synthetic inhibitors of nucleotide synthesis (methotrexate and 5-fluorouracil), nucleoside analogs (HPMPC / cidofovir and its derivatives with better bioavailability), interferon-alpha and inducers of interferons such as Imiquimod. Bevacizumab (Avastin) is a monoclonal antibody inhibitor of vascular endothelial growth factor (VEGF-A) that promotes the angiogenesis that supports papilloma growth. The most effective immunotherapy to date is mumps (or MMR) vaccine injected into a wart to trigger a local immune response with collateral impact on HPV. Ongoing effects in several labs are evaluating anti-E6/E7 immunotherapies augmented with enhancers of immune response.

Methods: High-grade dysplasias, carcinomas with integrated HPV DNA and metastatic HPV cancers justify far more aggressive chemotherapies, including the DNA cross-linking agents Carboplatin, Cisplatin and Mitomycin C, various topoisomerase I inhibitors derived from the natural tree bark product camptothecin (Topotecan and Irinotecan) and related DNA intercalating dyes, Gemcitabine and other nucleoside analogs or alkylating agents (Ifosfamide) that block DNA repair pathways, microtubule disrupters (taxanes such as Docetaxel and Paclitaxel) as well as antibodies that target for inactivation PD1 and PD-L1, which suppress the proliferation of antigen-specific T-cells.

Results: Our lab is actively using three-dimensional organotypic epithelial raft cultures comprised of (1) primary human keratinocytes harboring productive HPV-18 infections, (2) HPV-16 and HPV-18 immortalized cell lines that form dysplastic tissues, or (3) HPV-16 cancer cell lines (CaSki, SiHa), all of which form 3D phenocopies of natural lesions. Our strategy has been to identify host cell proteins and pathways on which HPV genome maintenance and replication depend, then to evaluate possible inhibitors of those processes and validate their efficacy, selectivity and safety, as described in other abstracts from our lab.

Conclusions: N/A

MSS 10 - Risk-based HPV screening: switching from one-size-fits-all programs to personalized screening programs

#0628

14 - Screening methods

EPIMETHEOS - AN OPEN SOURCE PLATFORM FOR RISK-BASED MODELING

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Background/Objectives: Many European countries have organized cervical screening programs, nevertheless the uptake of screening remains moderate in subpopulations at high risk whereas costs related to screening are high. Therefore, there is an urgent call for optimization of cervical screening programs, in particular because cervical cancer is on the rise in several countries. Current cervical screening programs, based upon one-size-fits-all protocol, are inefficient for vaccinated birth-cohort, provide suboptimal protection against cancer, lead to suboptimal allocation of resources and substantial screening- and treatment-related harms. The EU RISCC consortium has been set up to develop risk-based screening methods for the prevention of cervical cancer.

Methods: We are developing an open source platform to develop effective and cost-effective risk-based screening algorithms based on screening history, vaccination status, as well as demographic and behavioral risk predictors. Predictive modelling will be conducted including the use of microsimulation models for disease progression in relation to multiple oncogenic HPV types. Health gains, screening-related harms, and costs of different risk-based programs will be compared. The platform will incorporate both a transmission dynamic component and a cancer progressionmodel. We will assess the effectiveness and efficiency of a range of cervical cancer screening algorithms adapted to specific risk profiles.

Results: We aim at providing generalizable estimates of effectiveness and cost-effectiveness of risk-based cervical cancer screening algorithms. The platform will be devised to accommodate for screening history, vaccination status, population vaccination coverage, and other risk factors as reported in a selected range of EU countries. The software developed to assess the impact estimates, along with technical guidance material, will be made available as an open source package to encourage the standardization of local planning and evaluation of risk-based screening algorithms.

Conclusions: The results of this modelling initiative will be instrumental to develop an open m-health/e-health informatics platform that allows implementation of risk- based screening into real-life screening programs. Furthermore, knowledge and technologies developed in the RISCC framework will be transferable to other countries committed to cervical cancer elimination.

SS 13 - Immune responses to HPV infection

#0472

4 - Immunology

SS. Immune responses to HPV infection : THE ROLE OF HLA-ALLELES AND HOST IMMUNITY

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Background/Objectives: Persistent high-risk human papillomavirus (HPV) infection has been associated with increased risk for cervical precancerous lesions and cancer. The host's genetic variability is known to play a role in the development of cervical cancer (CC).

Methods: The human leukocyte antigen (HLA) genes are highly polymorphic and have shown to be important risk determinants of HPV infection persistence and disease progression. HLA class I and II cell surface molecules regulate the host's immune system by presenting HPV-derived peptides to T-cells. The activation of T-cell response may vary depending on the HLA allele polymorphism. The engagement of the T-cell receptor with the HPV peptide-HLA complex to create an active costimulatory signal is essential for the activation of the T-cell response.

Results: Different HLA alleles and their polymorphisms have been shown to be involved in the natural history of HPV infection. Some of these HLA alleles have been evaluated more for their potential to also be a biomarker for cervical carcinogenesis. The nonclassical class I HLA-G alleles could possibly be a successful biomarker for CC due to the relatively low HLA-G polymorphism and its several inhibitory and activator effects for protein expression for the innate and adaptive immune reactions. It has been shown that HLA-G plays a central role in the progression of the disease development, especially from preinvasive to invasive squamous CC

Conclusions: Functional peptide presentation by both HLA class I and II molecules is needed to activate efficient helper and effector T-cell responses in HPV infection recognition and clearance. Some of these HLA risk alleles could also be used as preventive tools in the detection of HPV-induced cervical lesions and cancer. HLA alleles, together with HPV vaccines, could potentially offer possible solutions for reducing HPV-induced cervical cancer as well as other HPV-related cancers.

CS 11 - How to act against fake news, anti-vaccination movements and manipulation of public opinion?

#0569

36 - Health education

Responding to anti-vaccination content on digital and social media: whose responsibility?

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Background/Objectives: A presentation on responding to vaccine misinformation on social media, using some examples from the world of fact checking. The presentation will cover the process of fact checking vaccine claims on social media as well as whose responsibility it is to fact check and moderate this content.

Methods: n/a

Results: n/a

Conclusions: n/a

References: n/a

#0247

38 - Public health

Using digital and social media as a positive tool to respond to public concerns

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Background/Objectives: Vaccine hesitancy is increasing and failure to vaccinate is well-recognised throughout the world as a contributing factor to outbreaks of infectious diseases. However, the time between infection, latency and oncogenesis can take many years with respect to HPV. Consequently, the impact of reduced HPV vaccine uptake due to misinformation, fabrication and stigma will be profound. It is incumbent upon all those involved in communicable disease to familiarise themselves with the tools to counter vaccine misinformation, while promulgating the remarkable impact of vaccines such as the HPV vaccines.

Methods: Trends in pro- and anti-vaccination discourse on social media such as Facebook and Twitter were examined. Belief systems and common themes were analysed with respect to HPV vaccine efficacy, safety and the stigma around HPV being a sexually transmitted infection.

Results: In a study by Gunaratne et al. (2019), all tweets between 2010 and 2019 containing vaccine-related hashtags were identified. Discussion subcommunities were identified with network analysis. 1,637,712 vaccine-related tweets were identified from 154 pro-vaccine and 125 anti-vaccine hashtags, with 86% of users posting exclusively pro-vaccine and 12% posting exclusively anti-vaccine hashtags. Pro-vaccine tweet volumes are larger than anti-vaccine tweets and consistently increase over time. In contrast, anti-vaccine tweet volumes have decreased since 2014, despite an increasing anti-vaccine user-base. Users infrequently responded across pro/anti-vaccine alignment (0.2%). Pro-HPV vaccine Twitterati tend to focus on female health, population-based data demonstrating high vaccine efficacy, and excellent vaccine safety profiles. In contrast, anti-HPV vaccine enthusiasts commonly focus on sporadic reports of potential vaccine injury, HPV being a virus that affects individuals through fault of their own with deplorable use of language, and interference by 'big pharma'.

Conclusions: Despite greater volumes of pro-vaccination discourse in recent years, and the anti-vaccination community being smaller, the anti-vaccine movement continues to grow in size, largely encouraged by social media. This finding coupled with the minimal inter-communication between communities suggests possible ideological isolation. Pro-vaccine Twitterati must strengthen their online communities of practice and challenge vaccine misinformation. Incorporation of HPV testing as part of screening will be an important step in de-stigmatising HPV through education, as will gender-neutral HPV vaccine programmes. Patient advocacy is a powerful lever in highlighting the importance of why we try to prevent HPV-driven cancers.

References: Gunaratne K, Coomes EA, Haghbayan H. Temporal trends in anti-vaccine discourse on Twitter. Vaccine. 2019 Aug 14;37(35):4867-4871. doi: 10.1016/j.vaccine.2019.06.086. Epub 2019 Jul 9.

SS 14 - HPV-based screening for cervical cancer

#0592

9 - HPV screening

o SS. HPV-based screening for cervical cancer / December, 7 / 08:00 - 09:30 / Title: Who is doing what: several countries that have introduced hpv screening or that have defined their future policies

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Background/Objectives: The Italian National Prevention Plan 2014-2019 established among the aims for the Regional Health Systems the complete transformation of the cervical cancer screening from Pap to HPV test. 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 (Ronco 2012).

Methods:

Results: In the period 2015-2018, 80% of the women aged 25-64 surveyed in the national health interview 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. In the last decade the proportion of coverage within organized programs increased. Geographical differences exists with higher uptake in Northern (88%) and Central (86%) than in Southern Italy (70%) (https://www.epicentro.iss.it/passi/dati/ScreeningCervicale). In 2017, more than 30% of the target population has been invited for HPV test by the screening programs, while the rest has been invited for Pap (47% in North, 33% in Centre and 8% in south). The proportion is increasing, being 8% in 2012 and 23% in 2016. Most of the programs started to invite to HPV testing older women. Most updated results on HPV-based screening programs in Italy comes from the cohort of women invited in 2016 and followed up until 2018, i.e. 458,416 screened women (www.osservatorionazionalescreening). HPV positivity was 7%, among HPV-positive 31.5% were cytology positive and referred to colposcopy. Compliance to 1-year retesting was 82.3%. HPV persistence at 1 year was 54.2%. The overall colposcopy referral was 4.1%, 2.1% immediately after cytology triage, 2.0% at 1-year HPV retesting. CIN2+ detection rate was 4.8/1000 screened women, and positive predictive value (PPV) was 13.1%. Most of the CIN2+ have been found at the baseline colposcopy where VPP was 19.4%, while in those referred to colposcopy because HPV-positive at retesting VPP was 6.3%. In the same period cytology screening had 2.9% colposcopy referral, 3.0/1000 detection rate and 16.6% PPV, but in a younger target population, where higher prevalence is expected. Data on second round from few programs are available, showing a decrease in colposcopy referral of more than 50% in women who tested negative in the previous round and a dramatic decre

Conclusions: In conclusion, the shift to HPV-based screening increased detection rate of persistent CIN2+, but also increased colposcopy referral. The most critical point of the protocol is how to manage HPV-positive/cytology-negative women. Women at second round have much lower colposcopy referral, but also low prevalence of disease.

References: Ronco G, Biggeri A, Confortini M, Naldoni C, Segnan N, Sideri M, Zappa M, Zorzi M, Calvia M, Accetta G, Giordano L, Cogo C, Carozzi F, Gillio Tos A, Arbyn M, Mejier CJ, Snijders PJ, Cuzick J, Giorgi Rossi P. Health Technology Assessment Report: HPV DNA based primary screening for cervical cancer precursors. Epidemiol Prev 2012;36 (Suppl 1):e1-e72 Del Mistro A, Giorgi Rossi P, Frayle H, Pasquale L, Campari C, Ronco G, Zorzi M. 5-year risk of CIN3 after short-term HPV-DNA negativity in cytology negative women: a population-based cohort study. JOG 2019;126:1365-1371. doi:10.1111/1471-0528.15893.

SS 15 - Validation of HPV assays for primary screening

#0465

8 - HPV testing

COMPARISON BETWEEN BD ONCLARITY, ROCHE COBAS, AGENA MASSARRAY HPV AND GENOMICA CLART HPV4 WITH SUREPATH CERVICAL SCREENING SAMPLES USING THE VALGENT FRAMEWORK

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Background/Objectives: Careful clinical validation of human papillomavirus (HPV) assays is increasingly important as primary HPV screening is replacing cytology-based cervical cancer screening. This VALidation of HPV GENotyping Tests (VALGENT) report evaluates four different HPV assays using a well annotated panel of samples collected in SurePath LBC media derived from the Danish Cervical Screening Programme. The four assays evaluated have limited (cobas), extended (Onclarity) or full genotyping capability (MassArray and CLART4s) which allows also for comparison on detection of HPV genotypes of relevance for cervical screening.

Methods: The VALGENT4 panel consists of 1,295 SurePath samples, 998 consecutive samples from routine screening enriched with 297 cytological abnormal samples. Original SurePath material was used for the Onclarity and cobas testing, whereas the MassArray HPV and CLART HPV4 assays require DNA as input material. The Onclarity and cobas assays are Real Time PCR assays, whereas the CLART4 is a PCR based microarray assay and the MassArray HPV assay is a PCR-based MassArray assay. The main objective was to verify non-inferior sensitivity and specificity of HPV testing with each assay compared to GP5+/6+ PCR EIA to detect CIN2+. The secondary objective was a detailed genotyping concordance analysis using the GP5+/6+ PCR Luminex as comparator.

Results: For the detection of CIN2+, the sensitivity and specificity estimates were 92.6% (CI: 86.5-96.6) and 91.1% (CI:89.1-92.9) for Cobas, 92.6% (CI: 86.5-96.6) and 92.6% (CI:90.7-94.3) for Onclarity, 96.7% (CI: 91.8-99.1) and 88.6% (CI: 86.4-90.6) for CLART4 and 94.3% (CI: 88.5-97.7) and 79.2% CI: 76.4-81.9) for MassArray. All four assays fulfilled the non-inferiority criteria for sensitivity and specificity at the exception of MassArray that fulfilled the sensitivity but not the specificity criterion.

Conclusions: Cobas, Onclarity and CLART4S assays all fulfilled the clinical accuracy criteria for cervical cancer screening, whereas the MassArray did not. The latter however, is an assay which allows for highly sensitive HPV genotyping in screening and other samples. The VALGENT4 study presents valuable performance data on HPV test with genotyping abilities using SurePath cervical cancer screening samples and the data from the study can be used to explore the use of genotyping in primary screening.

SS 16 - Update on next generation sequencing research

#0555

12 - Molecular markers

MICRORNA MARKER DISCOVERY BY GENOME-WIDE SMALL RNA SEQUENCING IN HPV-POSITIVE SELF-SAMPLES

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Background/Objectives: Offering self-sampling for HPV testing improves the effectiveness of current cervical screening programs by increasing population coverage. Molecular markers directly applicable on self-samples are needed to stratify HPV-positive women at risk of cervical cancer (so-called triage) and to avoid over-referral and overtreatment. Deregulated microRNAs (miRNAs) have been implicated in the development of cervical cancer, and represent potential triage markers. However, it is unknown whether deregulated miRNA expression associated with cervical disease is reflected in self-samples. This study is the first to establish genome-wide miRNA profiles using small RNA sequencing (sRNA-Seq) in HPV-positive self-samples to identify miRNAs that can predict the presence of CIN3 and cervical cancer in self-samples.

Methods: sRNA-Seq was conducted to determine genome-wide miRNA expression profiles in 74 HPV-positive self-samples of women with and without cervical precancer (CIN3). The optimal miRNA marker panel for CIN3 detection was determined by GRridge, a penalized method on logistic regression. Six miRNAs were validated by qPCR in 190 independent HPV-positive self-samples (101 controls, 48 CIN3, and 41 squamous cell carcinomas (SCCs)).

Results: Classification of sRNA-Seq data yielded a 9-miRNA marker panel with a combined Area Under the Curve (AUC) of 0.89 for CIN3 detection. Validation by qPCR resulted in a combined AUC of 0.78 for CIN3+ detection. Importantly, almost all SCCs (38 out of 41) were detected by our miRNA marker panel. Furthermore, sRNA seq has revealed that, in some cases, miRNA isoforms, so-called isomiRs, rather than the canonical miRNA sequence, are associated with disease progression.

Conclusions: This study shows the feasibility of conducting sRNA-Seq for miRNA quantification on HPV-positive self-samples and has identified a panel of miRNAs associated with CIN3 and cervical cancer. Validation by qPCR indicates that miRNA expression analysis on HPV-positive self-samples can be used in the management of HPV-positive women and may facilitate further implementation of self-sampling in cervical cancer screening programs. Interestingly, sRNA-Seq has revealed the presence of altered isomiR patterns associated with disease progression and indicates the potential diagnostic value of isomiRs in cervical samples.