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SHARED CHALLENGES OF HPV DRIVEN CANCERS
FROM RESEARCH TO PRACTICE

Congress Presidents | **Jesper Bonde (Denmark) • Jennifer S. Smith (USA)**

ABSTRACTS

MAIN CONGRESS PROGRAM

CS02- Test of cure: strategies for the follow up of women treated for cervical intraepithelial neoplasia

Jeannot Emmanuelle
France

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France

#5881

CIRCULATING DNA: A PREDICTOR OF SURVIVAL AND OUTCOMES AFTER TREATMENT FOR PRE-INVASIVE CERVICAL DISEASE AND CANCER

15 - Molecular markers

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Background/Objectives: Almost all cervical cancers (CC) are caused by human papillomavirus (HPV). Chemoradiotherapy is the current standard care for locally advanced cervical cancer but patients with advanced stage are at high risk for relapse. Circulating HPV DNA (HPV ctDNA) may serve as a residual tumor marker at the end of chemo-radiation or may predict relapse during the follow-up period. Additionally, HPV ctDNA may serve to identify patients with cervical dysplasia at risk of malignant transformation.

Methods: We analyzed serum samples from patients with HPV16- or HPV18-related CC or cervical intraepithelial neoplasia (CIN) 3. Samples were collected before and after treatment in the CC group. Only serum samples collected before treatment were available in the CIN3 group. We used digital droplet PCR (ddPCR) to detect circulating HPV DNA and to assess its prognostic impact as well as its prediction value of relapse.

Results: Circulating HPV DNA (HPV ctDNA) was detected in 63% (59/94) of patients with CC, before treatment. HPV ctDNA detection in serum sample was associated with high FIGO stage (p=0.02) and para-aortic lymph node involvement (p=0.01). Complete clearance of HPV ctDNA by the end of treatment was significantly associated with a longer PFS (p<0.0001) in both cohorts. Analysis of additional serum samples taken during follow-up showed that patients with persistent HPV ctDNA in serum relapsed with a median time of 10 months (range, 2-15) from HPV ctDNA detection. There was no HPV ctDNA detection in serum from patients with CIN3 (0/18).

Conclusions: Circulating HPV DNA may be a useful marker to identify patients at risk of relapse of CC. Additional studies are required to assess the potential of this marker to identify patients with lesions at risk of malignant transformation.

PC- Opening Ceremony with Young Scientist Pitch Competition

Rozemeijer Kirsten
Netherlands
Rozemeijer Kirsten
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#4938

METHYLATION ANALYSIS OF ANAL SWABS: THE FUTURE OF ANAL CANCER SCREENING?

28 - Anal neoplasia

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Background/Objectives: Currently, only a subset of high risk groups in the Netherlands are screened for anal cancer due to limited capacity and limited expertise of high resolution anoscopy (HRA). Furthermore, screening by HRA is cost some and burdensome for the participant. Hence there is an urgent clinical need for an objective minimally-invasive screening test on anal swabs. We previously showed that testing for DNA methylation markers on anal biopsies can accurately detect high-grade AIN at risk of progression to anal cancer, referred to as advanced HGAIN(1). Here, we examined the feasibility and performance of methylation testing on anal swabs. Results are compared and combined with high-risk HPV (hrHPV) testing and cytology. Besides the methylation markers previously tested on biopsies, also a genome wide methylation analysis on anal swabs is performed to discover most discriminatory methylation markers on swabs.

Methods: We prospectively collected anal swabs and paired biopsies of 223 HIV+ men who have sex with men (MSM) in screening for anal cancer and 20 patients diagnosed with anal cancer. DNA methylation levels were measured for 6 markers in both swabs and biopsies, if present, and compared between histological outcomes using Mann-Whitney test. hrHPV testing and cytology testing were performed on all swabs. Area's under the curve (AUCs) were determined using logistic regression analysis. Cases were defined as advanced HGAIN (i.e., methylation positive HGAIN). Genome wide methylation profiling was performed on anal swabs of 40 HIV+ MSM diagnosed with AIN3 (i.e., cases) and 40 HIV+ MSM diagnosed with <AIN1 (i.e., controls), using the 850K Infinium MethylationEPIC BeadChip (Illumina).

Results: Absolute median methylation levels were significantly higher for all 6 markers in cancer swabs as compared to control swabs. For the detection of advanced HGAIN, marker ZNF582 performed best with an AUC of 0.69 (95% CI: 0.60-0.79). The addition of this marker to combined hrHPV testing and cytology testing increased the AUC from 0.77 (95% CI: 0.71-0.83) to 0.83 (95% CI: 0.76-0.90). Preliminary results of our genome wide methylation analysis indicate that alternative methylation markers may be valuable for screening for advanced HGAIN on anal swabs.

Conclusions: Testing for DNA methylation markers on anal swabs is feasible. Methylation levels increase with severity of underlying lesions and are extremely high in swabs of anal cancer patients. Current methylation markers combined with hrHPV and cytology testing detect advanced HGAIN with an AUC of 0.83. Newly discovered methylation markers may increase test performance, thereby allowing for objective anal cancer screening on anal swabs.

References: R. van der Zee et al. Cancer Risk Stratification of Anal Intraepithelial Neoplasia in Human Immunodeficiency Virus-Positive Men by Validated Methylation Markers Associated With Progression to Cancer. Clin Infect Dis. 2021;72(12):2154-2163.

Ellis Laura
United Kingdom

Ellis Laura
United Kingdom

#4799

Diagnostic Accuracy of Human and Human Papillomavirus DNA Methylation Testing in Cervical Cancer: A Systematic Review and Meta-Analysis

18 - Methylation

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Background/Objectives: Cervical cancer is the fourth most common malignancy in women worldwide. Current cervical screening programmes use a primary screening test of high-risk HPV (hr-HPV) testing or cytology to identify at risk women. hrHPV testing has a high sensitivity but low specificity for high-grade CIN and Cancer. As a result, DNA methylation testing has been suggested as a triage test for hrHPV positive women. As yet, there is no consensus on the most accurate methylation markers for use in screening. We conducted a systematic review and meta-analysis to determine the diagnostic test accuracy of human and HPV DNA methylation markers.

Methods: MEDLINE, EMBASE, and ongoing trial registries were systematically searched from inception to February 2022. DNA methylation diagnostic test accuracy studies using histopathology as a reference standard were included. Sensitivity and specificity data were extracted: a bivariate random-effects model was applied to calculate pooled estimates and corresponding heterogeneity, which was explored in a series of sensitivity analyses.

Results: Twenty-eight studies including 6,956 women were meta-analysed, producing pooled estimates for genes C13ORF18, EPB41L3, FAM19A4, HPV16:L1, JAM3, PAX1, SOX1, and ZNF582. PAX1 was the most accurate marker of CIN2+ with a pooled area under the curve (AUC) of 0.93 (95% confidence interval (CI) 0.90-0.95) and pooled AUC of 0.87 (95%CI 0.84-0.90) for CIN3+. HPV16:L1 was the second-best marker of CIN2+; pooled AUC 0.83 (95%CI 0.80-0.86). JAM3 was the most accurate marker of CIN3+; pooled AUC 0.88 (95%CI 0.85-0.91).

Conclusions: PAX1 methylation testing appears to be the most accurate methylation marker for high-risk CIN and Cancer. Specificity may surpass cytology allowing the potential to triage patients more effectively to colposcopy or conservative management. Our analysis has also elucidated several other genes which show promise for use in methylation marker panels; combined panels may provide greater accuracy than stand-alone methylation markers.

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#4897

Profiling HPV antibody responses 6 years following 1, 2 or 3 doses of quadrivalent HPV vaccine

06 - HPV prophylactic vaccines

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Background/Objectives: The World Health Organisation recently gave a permissive recommendation for HPV vaccine of 1 or 2 doses for females <20 yo. This was based on evidence demonstrating comparable vaccine efficacy between 1 or 2 doses, despite 1 dose inducing lower neutralising antibody levels. No immune correlate has been identified, and neutralising activity is thought to be the mechanism of vaccine protection. However, antibodies have multiple effector functions mediated by Fc receptors (FcR), which may contribute to vaccine-induced protection. Therefore, we profiled HPV-specific antibody features including FcR engagement in girls who received 1, 2 or 3 doses of quadrivalent HPV vaccine (4vHPV) 6 years earlier and their booster responses after bivalent HPV vaccine (2vHPV).

Methods: In 2015, a prospective cohort study was conducted in 200 Fijian girls (15-19 yo) who were previously unvaccinated or received 1, 2 or 3 doses of 4vHPV 6 years prior. Blood was collected pre- and 28 days post-2vHPV. Using a multiplex immunoassay, antibody isotypes and subclasses (total IgG, IgM and IgG1-4, IgA1-2) and FcR-binding (FcγRIIa, FcγRIIb, FcγRIIIa) were measured against HPV16/18 and 5 vaccine-related genotypes in the nonavalent vaccine (HPV31/33/45/52/58) in a subset of participants (N=20/group).

Results: After 6 years, 1-dose 4vHPV recipients had significantly lower HPV16/18 IgG mean fluorescence intensity (MFI) compared to recipients receiving 2 or 3 doses ($p<0.05$). However, HPV16/18 IgG and IgA1 MFI in 1-dose recipients were significantly higher than unvaccinated girls ($p<0.05$). Antibody subclass profiles were similar between 1-, 2- and 3-dose recipients, with high IgG1, IgG3 and low IgM, IgA responses. Following a booster dose of 2vHPV, HPV16/18 antibody responses in 1-dose 4vHPV recipients increased to a similar level and subclass profile as 2- or 3-dose recipients. We found differences in antibody profiles against HPV16 and HPV18, with total IgG comprising mostly of IgG1 and IgG3 for HPV16 but predominantly IgG1 for HPV18 in 4vHPV recipients. Similarly, moderate IgA1 responses were observed post-2vHPV for HPV16 but not HPV18. For closely-related non-vaccine genotypes (HPV16; HPV31/33/52/58, HPV18; HPV45) there were weaker responses but similar antibody subclass profiles. Type-specific FcR engagement analyses are currently ongoing.

Conclusions: A single dose of 4vHPV induced HPV type-specific antibodies of similar subclass profile to 2 or 3 doses which persisted for at least 6 years. Future work to evaluate Fc-mediated antibody effector functions will improve our understanding of HPV vaccine immune mechanisms.

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#4940

IMPACT OF MOBILE GAME FIGHTHPV ON CERVICAL CANCER SCREENING ATTENDANCE: RETROSPECTIVE COHORT STUDY

38 - Health education

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Background/Objectives: In 2019, the World Health Organization released the first evidence-based guideline on scaling up the usage of technological applications to reduce health inequities and introduce a new era to healthcare, since the availability of mobile phones has made the dissemination of health-related information easy and accessible. Gamification is an innovative approach that motivates people to acquire new knowledge in a fun and engaging way, and it has proven to be a successful knowledge translation tool. With gamification, mobile apps can nudge people to make informed health choices, including attending cervical cancer screening. We developed an innovative game-based mobile phone learning tool named FightHPV to educate its users about cervical cancer, its main causal agent, human papillomavirus (HPV), and its prevention. In this matched retrospective cohort study, we examined the association between exposure to the FightHPV mobile app gamified educational content and having a cervical exam in the following year.

Methods: Women aged 20-69 years who signed an eConsent after downloading the FightHPV app in 2017 (intervention group) were 1:6 matched with women who had the same age and the same screening history (reference group) in 2015. To estimate the FightHPV app impact, we estimated cumulative incidence and hazard ratios (HRs) with 95% confidence intervals (CI). We used data from the Norwegian Cervical Cancer Screening database and Statistics Norway.

Results: For 658 women in the intervention group, we matched 3860 controls. 1-year after enrollment, 44.2% (95% CI 30.3-47.9%) in the intervention group and 27.0% (95% CI 25.6-28.4%) in the reference group underwent a cervical exam ($p<0.01$). 6 months after enrollment, women exposed to the FightHPV app were 2-times more likely to attend the screening (adjusted HR 2.3, 95% CI 2.0-2.7) and were diagnosed almost 13-times more with high-grade lesions (adjusted HR 12.7, 95% CI 5.0-32.5) as compared to the women in the reference group.

Conclusions: To our knowledge, the FightHPV app is the first-ever game-based health-related information intervention tool developed to increase demand for cancer screening among the screening program target population. The FightHPV app gamified scientifically accepted principles of cervical cancer prevention to augment processing and contextualizing health information, with an ultimate goal to nudge the player to attend screening. FightHPV app exposure significantly increased attendance to cervical cancer screening across the various analyses and improved the detection of women with high risk for cervical cancer. For the first time, we demonstrated the effectiveness of gamification combined with mobile technology in cancer prevention by empowering women to make active health-related decisions. Gamification can significantly improve the understanding of complicated scientific concepts behind interventions and increase the acceptance of proposed cancer control measures.

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United States

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#4795

Oral Human Papillomavirus prevalence and risk factors among healthy populations attending routine dental care in the United States: Results from the PROGRESS (PRevalence of Oral hpv infection, a Global aSSessment) study

03 - Epidemiology and natural history

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Background/Objectives: In the United States (US) oropharyngeal squamous cell carcinoma is the most frequent HPV-associated cancer, surpassing cervical cancer. Oral HPV prevalence and genotype distribution can inform the burden of HPV-related head and neck diseases and planning of effective prevention programs. This study assessed oral HPV prevalence and risk factors in a general US population.

Methods: Between November 2021 and March 2022, 18-60-year-olds were recruited from 42 dental offices across the US. Participants provided oral rinse and gargle specimen for HPV-DNA detection and genotyping and completed sociodemographic and behavioral questionnaires. HPV-DNA detection and genotyping was performed using the SPF10/DEIA/LiPA25 system at a central laboratory.

Results: Of the 3,180 participants enrolled, 55.4% were women, with a median age of 40; 12.2% self-reported having received HPV vaccination. Oral HPV prevalence was 6.5% for any detected genotype, 2% for high-risk types, 1.5% for HPV types in the 9-valent HPV vaccine, and 0.7% for HPV16. Among oral HPV positive participants, HPV 16 was the most prevalent genotype (10.6%) followed by HPV 51 (7.2%) and HPV 66 and 44 (both 5.8%). HPV prevalence was higher in men (9.0%) than women (4.5%), and increased with age with 3.1%, 5.5%, 5.1% and 11.8% prevalence among ages 18-30, 31-40, 41-50 and 51-60, respectively. When stratified by sex and age, HPV was most commonly detected among men aged 51-60 (16.8%). Factors significantly associated with any high risk HPV infection included sex, age, smoking status, lifetime number of sex partners, and presence of periodontal disease.

Conclusions: The highest oral HPV burden was among older men, highlighting the need to increase HPV prevention efforts among males. Prevalence and risk factors in the US will be compared to PROGRESS studies currently being conducted in Europe and China using similar methodologies to increase knowledge of the global oral HPV burden.

De Carvalho Tiago M
Netherlands

De Carvalho Tiago M.
Netherlands

#4717

Health and economic effects of introducing single-dose human papillomavirus vaccination in India.

36 - Economics and modelling

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Background/Objectives: Cervical cancer is a major public health problem in India, where access to prevention programmes is low. The World Health Organization (WHO)-Strategic Advisory Group of Experts recently updated their recommendation for human papillomavirus (HPV) vaccination to include a single-dose option in addition to the two-dose option, which could make HPV vaccination programmes easier to implement and more affordable.

Methods: We combined projections from a type-specific HPV transmission model and a cancer progression model to assess the health and economic effects of HPV vaccination at national and state-level in India. The models used national and state-specific Indian demographic, epidemiological and cost data, and single-dose vaccine efficacy and immunogenicity data from the IARC India vaccine trial with 10-year follow-up. We compared single- and two-dose HPV vaccination for a range of plausible scenarios regarding single-dose vaccine protection, coverage and catch-up.

Results: Under the base-case scenario of life-long protection of single-dose vaccination in 10-year-old girls with 90% coverage, the total cost of introducing single-dose HPV vaccination was ₹INR 7.8 billion ($USD 106 million) in the first year, equivalent to 9% of the annual cost of the Indian universal childhood vaccination programme. The incremental cost-effectiveness ratio (ICER) of nationwide vaccination relative to no vaccination was ₹INR 30 thousand per DALY averted (state-specific ICER range: ₹INR 5-44 thousand,) and lay below an opportunity-cost based threshold of 30% Indian GDP per capita (₹INR 44 thousand). The ICER of two-dose vaccination versus no vaccination was ₹INR 104 thousand (70% of the Indian GDP per capita). The ICER of two- versus single-dose vaccination was minimum ₹INR 169 thousand. This is above the ₹INR 148 thousand threshold (100% Indian GDP per capita) corresponding to the WHO threshold.

Conclusions: Nationwide introduction of single-dose HPV vaccination in India is highly likely to be cost-effective whereas extending the number of doses from one to two would have a less favourable profile. These results could convey several lessons for implementation in other LMICs.

SS09- Tumour HPV status and implications for survival outcomes in cervical and non-cervical disease

Lassen Pernille
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#5898

Lecture: Treatment de-intensification of oropharyngeal disease - navigating the data from trials

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The emergence of human papillomavirus-related (HPV+) oropharyngeal cancer (OPC) has changed the landscape and conventional understanding of the clinical behavior of squamous cell carcinoma of the head and neck (HNSCC). Compared to traditional HPV-negative HNSCC, HPV+ OPC represents a unique subgroup with very different epidemiology and patient risk-profile, molecular biology, and response to radiotherapy/chemo-radiotherapy (RT/CRT). Excellent disease control but significant toxicity burden with CRT has stimulated the design of clinical trials for over the past decade, to explore the possibility of deintensification for "low-risk" patients. However, the first putative "deintensification' strategy substituting cisplatin with EGFR-inhibitor failed to show improvement in toxicity and, even worse, compromised outcome with higher locoregional failure (LRF) and worse survival in three randomized trials, prompting concern over the feasibility of de-escalation. Consequently, CRT remains the standard of care for advanced OPC regardless of HPV-status, and deviation from this should only be done within the frames of clinical trials. The talk will cover some general aspects on the radiobiological modifications of radiotherapy that have resulted in improved outcomes for OPC over the past 35 years, including a discussion of the (smoking related) molecular and genetic heterogeneity among HPV+ tumors, which ultimately impacts their radiosensitivity and treatment response. Furthermore, selected de-escalations principles (chemotherapy attenuation, morbidity optimized radiotherapy and upfront surgery for early stage OPC) will be discussed along with results from relevant trials and meta-analyses.

Methods: N/A

Results: N/A

Conclusions: N/A

HN01- HPV and H&N Forum - Screening for HPV-OPC

Pimenoff Ville
Sweden

Lehtinen Matti
Sweden

#5047

Relation of prediagnostic HPV16 E6 antibodies with oropharyngeal cancer over the last 40 years

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Prediagnostic antibodies to human papillomavirus (HPV) type 16 are associated with a 15-fold relative risk(RR)to develop oropharyngeal squamous cell cancer (OPSCC) within 10 years, and the HPV16 associated population attributable fraction in oropharyngeal cancer has continuously increased during the last decades. Notably, antibodies to HPV16 early E6 protein can be positive up to 25 years before the OPSCC diagnosis.

Methods: We performed parallel nested case-control and a case-cohort studies in the FMC (Finnish Maternity Cohort) -serum bankto evaluate the use of prediagnostic E6 serology in the diagnosis of oropharynegal cancer (OPC). Linkage between the FMC serum bank and Finnish Cancer Registryprovided up to 35years of follow up post serum sampling.113OPC cases with prediagnostic sera were identified, and i) 1:1 age-matched with controls, who did not develop OPC during the follow-up, or ii) compared to a control cohort of 730 women stratified by age at serum sampling, calendar-time and season of sampling, and residence. Relative risk (odds ratio, OR with 95% confidence interval) estimates associated to HPV16/33 early E1, E2, E6 and E7 protein antibody positivity and/or to HPV16 and 33 L1 virus-like-particle (VLP) antibody positivity were compared between the parallel study settings.

Results: Applying two different cut-off level for the HPV16 E6 serology (MFI: 484 and 1000) we found, respectively statistically highly significant (OR=23, 95%CI 3.1-180) and/or 100% specific associations between the E6 antibody positivity and OPC. The case-cohort study helped to identify when the disease association started to become stronger. Adding up antibody positivity for other HPV E-proteins increased the odds without loss of the combined test specificity.

Conclusions: HPV16 E6 antibody testing in healthy, fertile-aged women is firmly associated with the risk for later diagnosis of oropharyngeal cancer.

HN02- HPV and H&N Forum- Basic science

Klein Sebastian
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#5856

Granular stratification of OPC patients using standard H&E staining

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell cancer (OPSCC/OPC) represents an OPSCC subgroup with an overall good prognosis with a rising incidence in Western countries. Multiple lines of evidence suggest that HPV-associated tumors are not a homogeneous tumor entity, underlining the need for accurate prognostic biomarkers.

Methods: Recently, we developed a deep learning-based approach to predict HPV-association using scans of regular H&E stains (Klein et. al.). The previous approach included a smaller dataset with a focus on prediction of HPV-status and comparison to human observers, lacking information on treatment modalities and different disease stages, as well as different tumor locations (primary/lymph node metastases). Within the current study, we aimed to build a modular algorithm that can be run at low computational costs to stratify OPSCC patients more accurately than HPV-testing by using regular H&E stained whole-slide-images and compared the performance to gold standard using different clinical scenarios.

Results: In this retrospective, multi-institutional study involving 906 patients from four centers and one database, we developed a deep learning algorithm, to analyze standard H&E stains for the calculation of a patient-level score associated with prognosis comparing it to combined HPV-DNA and p16-status. When comparing this algorithm to HPV-status, the algorithm showed a good overall performance with a mean area under the receiver operator curve (AUROC)=0.83 (95% CI=0.77-0.9) for the validation cohorts (n=639), which could be increased to AUROC=0.88 by filtering cases using a potential surrogate marker of HPV-heterogeneity. The algorithm could be used as a screening tool, outperforming gold standard HPV-testing (algorithm: five-year survival rate: 96% [95% CI=90-100%]; HPV-testing: five-year survival rate: 80% [95% CI=71-90%]). This could be confirmed using a multivariate analysis of a three-tier threshold (algorithm: high HR=0.15 [95% CI=0.05-0.44], intermediate HR=0.58 [95% CI=0.34-0.98], p=0.043, n=211; HPV-testing: HR=0.29 [95% CI=0.15-0.54] p<0.001; n=211).

Conclusions: Together we show, that by analyzing standard gigapixel H&E histological whole-slides, the algorithm can identify OPSCC patients with a favorable prognosis, oupterforming p16/HPV-DNA testing in several clinical scenarios including early- and late stage OPSCC, as well as its applicability on lymph node metastases.

References: Klein, S., et al. Deep learning predicts HPV-association in oropharyngeal squamous cell carcinomas and identifies patients with a favorable prognosis using regular H&E stains. Clin Cancer Res (2020).

MSS10- Impact of HPV vaccine on cancer

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#5890

Effectiveness of HPV vaccination: a Swedish perspective

06 - HPV prophylactic vaccines

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Background/Objectives: Several studies have demonstrated the population effectiveness of quadrivalent HPV (qHPV) vaccination against genital warts, cervical precancerous lesions and invasive cervical cancer (ICC). We evaluated the effectiveness of qHPV vaccination against high-grade lesions and ICC with an extended follow-up period.

Methods: We investigated the effectiveness of HPV vaccination against high-grade lesions and ICC in a national cohort study of women of around 1.7 million aged 10-31 years during 2006-2018 utilizing Swedish registries. Girls and women that had at least one dose of qHPV vaccination were considered as vaccinated, and HPV vaccination was assessed as a time-varying exposure. We investigated the association between HPV vaccination and the risk of cervical intraepithelial neoplasia grades 2 or worse (CIN2+) and ICC, controlling for age at follow-up, calendar year, county of residence, and parental characteristics, including education, household income, mother's country of birth, and maternal disease history. Incidence rate ratios (IRR) with 95% confidence intervals (CI), were estimated in Poisson regression models.

Results: A total of 572,180 women (26.9%) had at least one dose of HPV vaccination. Compared to not vaccinated women, the fully-adjusted IRR against CIN2+ was 0.28 (95% CI 0.22 - 0.34) for women vaccinated before age 14, 0.48 (CI 0.46 - 0.51) for women vaccinated at age 14-16, 0.65 (CI 0.62 - 0.69) for women vaccinated at age 17-19, and 0.93 (CI 0.88 - 0.98) for women vaccinated at age 20-31, respectively. The IRR for HPV vaccinated vs. unvaccinated women against ICC was 0.38, (CI 0.26 - 0.57) after adjusting for all covariates. For women vaccinated before age 17 and at ages 17-30 fully-adjusted IRRs of ICC were 0.23 (CI 0.10 - 0.53) and 0.45 (CI 0.29 - 0.70), respectively.

Conclusions: In this extended follow-up, qHPV vaccination was associated with a substantially reduced risk of high-grade lesions and invasive cervical cancer at the population level. Greater risk reduction was observed for girls vaccinated at younger age.

SS13- New triage methods

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#4825

ASSESSMENT OF TRANSVERSAL ACCURACY FOR CIN3+ LESIONS OF HPV GENOTYPING USING THE BD ONCLARITY HPV ASSAY IN CERVICO-VAGINAL SAMPLES FROM THE NTCC2 STUDY

14 - Genotyping

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Background/Objectives: The oncogenic potential is different for each of the High Risk HPV genotypes, and the risk of having a CIN3+ varies according to genotype. We evaluated the accuracy for CIN3+ of HPV genotyping using the BD Onclarity HPV Assay in cervico-vaginal samples from the Italian NTCC2 study.

Methods: Samples of the NTCC2 study that were baseline HPV-DNA positive with Cobas or HC2 assay, were analyzed by the BD Onclarity HPV Assay, using 0.5 mL of the Thin Prep sample stored in the NTCC2 biobank. HPV-DNA positive women were followed up for 24 months or to clearance.

Results: Among the 3129 Cobas/HC2 baseline HPV-DNA positive samples 667 were Onclarity positive for HPV16/18 genotypes and, among them, we found 56 CIN3+, whereas 2462 were Onclarity non-HPV16/18 positive. Among these 2462 women, 550 had an ASC-US+ cytology triage report and were submitted to immediate colposcopy where 27 CIN3+ were found;1879 had NILM triage cytology and were randomized as for the NTCC2 protocol to immediate colposcopy or 1-year HPV retesting. Among all of them, 13 CIN3+ lesions were found. Regarding the CIN3+ prevalence and the HPV 1-year persistence, the cases can be divided into three groups based on the Onclarity genotyping results: 1. High Risk (HR) including genotypes 45, 33/58, 31 and 52 (n=644) where we found 10 out of the 13 CIN3+ lesions (77%); 2. Low Risk (LR) including genotypes 51, 35/39/68, 56/59/66 (n=584) where only 2 CIN3+ were detected; and 3. HPV negative (n=651) where only 1 CIN3+ was disclosed. In the baseline HPV-DNA positive/cytology negative women who were retested at 1 year, HPV persistence according to Onclarity genotyping was 71%, 48.6% and 26.6% respectively in the three groups. A total of 2279 out of the 2462 BD non-HPV16/18 positive women were tested with p16/ki67 dual staining: 532 were p16/ki67 positive, and among them 30 CIN3+ were found. Among the 1747 p16/ki67 negative, 537 women were positive for HR HPV, and among them 6 CIN3+ were detected; 578 were positive for LR HPV, with 2 CIN3+, and 632 were BD negative, with 2CIN3+. HPV persistence at 1-year according to Onclarity typing was 72.1%, 40,1% and 33.7% respectively.

Conclusions: Among the women with baseline HPV-DNA positive/cytology or p16/ki67 negative results, the Onclarity HPV Assay allows to stratify for immediate risk of CIN3+ and to predict HPV clearance at 1 year. Furthermore, in women cytology or p16/ki67 negative and with HPV 56/59/66 or 35/39/68, it can identify a group with a very low risk of CIN3+ in the next 2 years. Women baseline HPV-DNA positive with Cobas/HC2 but negative with the Onclarity test showed the lowest CIN3+ risk.

SS14- Screening and vaccination implementation in Eastern and Central Europe – a part of Europe with the highest burden of cervical cancer

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#5842

Implementation status of national organised HPV-based cervical cancer screening in Albania

13 - Self-sampling

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Background/Objectives: Screening performance, sensitivity and specificity, is comparable between self-collected and practitioner-collected samples for HPV screening [1]. Therefore, self-collection has the potential to improve coverage and convenience in HPV-based screening programs [2]. Self-collection provides an avenue for increased accessibility to cervical cancer screening and is seen to improve screening rates for individuals who are typically under-screened by reducing logistical and personal barriers encountered with clinician-based screening [3,4]. Furthermore, self-collection has the potential to offer a more convenient and acceptable form of screening for all individuals, including those who are already engaged in routine screening [5]. For the successful integration of self-collection in screening programs for all screen-eligible individuals, there is a need to evaluate willingness and acceptability of self-collection in the well-screened population [6]. The National Cervical Cancer Screening Program in Albania iniciate in 2019, targets women 40-50 years old, based the high risk HPV self-sampling. The screening program will improve identification in time the pre-cancer lesions, and treat them accordingly. Self-collection may provide an opportunity for innovation within population-based HPVcervical cancer screening programs by providing an alternative form of engagement for all Albanian women population. The primary objective was to determine willingness to self-collect a vaginal sample for primary HPV screening and factors that impact willingness in individuals who participated in the HPV Cervical Cancer screening program

Methods: A cross-sectional survey evaluation on a representative sample of women, users of the program, (200 women), was distributed at the end of the first year of implemented program in Albania 2019 to 200 random participants from 10 000 women screened in Albania. Descriptive analysis assessed factors that influence willingness to self-collect on 198 respondents.

Results: Overall, with it 67% of respondents indicated willingness to self-collect an HPV sample and, 33% of women in the sample reported to have asked the physician to help them. Younger women (44.6 of the 40-44 years old) have been more inclined to ask the personnel to get the vaginal sample than (30% of 45-49 years old). The majority of women found the vaginal sampling procedure very simple (60%) and not at all painful (72%). Around 8% of them reported it to be difficult. The overall rating of the service at primary health care centre, by women who have used it, is "good' or "very good', only 11% of women consider it average or bad (respectively 7% and 4%).

Conclusions: HPV self-sampling is generally a highly accepted method of cervical cancer screening proved to be an effective way to increase participation in screening program in Albania. Despite its potential benefits, the implementation of vaginal self-sampling has challenges, including healthcare workers training to explain the self-sampling procedure adequately to participating women, transportation of the collected specimens, and finally, skilled clinicians to manage and follow-up positive women.

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HN06- HPV and H&N Forum - Submitted papers 2

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#4533

RISK-ADAPTED THERAPY IN HPV+ OROPHARYNGEAL CANCER TUMOR-TISSUE MODIFIED VIRUS (TTMV)-HPV DNA PROFILE | THE REACT STUDY

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: An increasing number of patients have HPV-associated squamous cell carcinomas of the oropharynx (OPC). For patients undergoing non-surgical treatment, the standard of care typically includes approximately 7 weeks of chemoradiation therapy (CRT). However, acute and long-term adverse effects are potentially severe and include mucositis, dysphagia, fibrosis, xerostomia, and dental problems. Given the excellent prognosis of this patient population, treatment de-intensification is of significant interest. There is debate as to which patients are most suitable for de-intensification. Phase 2 data suggest favorable results for various de-intensification strategies among clinically low risk patients, but more variable results among patients with higher risk features such as tobacco use or T4 disease. Thus, novel strategies are needed to better identify which OPC patients are best suited for de-intensified treatment. Circulating tumor (ct)DNA is released by cancer cells and is an accessible source for detecting tumor genetic biomarkers. A recent prospective biomarker study showed a 100% negative predictive value using a validated droplet digital (dd)PCR assay (NavDx®) for high-risk HPV strains (Naveris, Waltham, MA), and all the patients with recurrence in the study had detectable tumor-tissue modified virus (TTMV)-HPV DNA post-treatment. Prior data also suggest that early clearance of TTMV during CRT predicts favorable outcomes, even in patients with clinical risk features such as tobacco use or T4 disease. Drawing from this evidence, the REACT study aims to use NavDx as a risk stratifying biomarker to identify ideal candidates for treatment de-intensification.

Methods: REACT is a phase 2 non-randomized exploratory study aimed at refining previously established risk groups for HPV+ OPC by coupling a patient's blood-based or circulating HPV DNA profile with clinical risk factors to guide treatment de-intensification. Clinically low-risk patients receive de-intensified CRT. Clinically intermediate risk patients (defined as T4 disease or >10 pack-year tobacco history) with: (1) baseline level >200 TTMV HPV copies/mL with (2) rapid clearance (>95% clearance by week 4 of treatment) receive de-intensified CRT. The primary aim of the study is to establish the ability of TTMV HPV DNA to select intermediate risk patients to receive de-intensified therapy as measured by 2-year progression-free survival (PFS) when compared to historical trial data. Secondary aims include assessing overall survival (OS) at 2-years, the rate of distant failure, best overall response, and patient quality of life outcomes. Exploratory aims include the relationship between decreasing TTMV-HPV DNA and on-treatment MRI imaging metrics.

Results: NA

Conclusions: TTMV HPV DNA represents a potential means to offer a personalized treatment de- intensification strategy for patients with HPV+ OPC. The trial is ongoing (NCT04900623).

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#4253

Detection of antibodies against HPV16 E6 oncoprotein by ELISA: validation of a new and promising biomarker for diagnosis of HPV-driven oropharyngeal cancer

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: In US and many European countries, human papillomavirus (HPV) has been a major factor in the incidence increase of oropharyngeal cancer (OPC), especially HPV16. However, there are no validated screening assays for the prevention of HPV-related OPC and diagnosis algorithms for HPV-related classification are still under evaluation. HPV16 E6 serology has become a promising biomarker for OPC early detection and diagnosis. This study aims to validate HPV16 E6 oncoprotein antibodies detected by ELISA (compared to Luminex) in a blood donor population and OPC diagnosed patients.

Methods: We retrieved 7,731 blood samples from donors of the Catalan blood bank [7,287 donors who are negative for hepatitis B and C, human immunodeficiency virus, syphilis and 444 donors who have at least one positive serology for these sexually transmitted diseases (STD)] and collected data and serum specimens at time of diagnosis from 170 OPC patients from two hospitals in Catalonia [118 OPC patients from a retrospective cohort from Hospital de Sant Pau and 52 cases from a prospective cohort from ICO-Hospitalet/Hospital University de Bellvitge]. HPV16 E6 antibodies were evaluated by ELISA and Luminex in blood donors and OPC patients; and HPV DNA, HPV mRNA E6*I and p16INK4a were assessed in OPC formalin-fixed paraffin embedded tissue blocks (FFPE). HPV-driven was defined by HPV DNA and p16 double positivity. Seroprevalence, and concordance of serological results by ELISA and Luminex were calculated by type of population. Moreover, in OPC patients, sensitivity and specificity of both serology techniques considering HPV biomarkers in FFPE were evaluated.

Results: The HPV16 E6 seropositivity was 11.0% for patients with OPC and 1.5% in the case of blood donors (1.5% for STD-free donors and 1.1% for STD-positive donors). Concordance between techniques was high (from 98.6%-blood donors to 99.2%-OPC patients). Sensitivity and specificity of HPV16 E6 antibodies for HPV-driven OPC was 80% [95%CI:52-96%] and 99% [95%CI:95-100%] for ELISA, 80% [95%CI:52-96%] and 98% [95%CI:93-100%] for Luminex.

Conclusions: HPV16 E6 seropositivity is a sensitive and highly specific biomarker for HPV-OPC, either by ELISA or Luminex technology. ELISA technique for HPV16 E6 detection shows high concordance with Luminex technique and could be used in large scale research studies and clinics, for prevention and diagnosis.

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SURVIVAL AND RECURRENCE OUTCOMES IN HPV+ OROPHARYNGEAL SQUAMOUS CELL CARCINOMA PATIENTS TREATED WITH TORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: To evaluate and analyze the literature available regarding transoral robotic surgery (TORS) survival and recurrence outcomes in human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC).

Methods: A systematic review (CINAHL, PubMed, Scopus) was performed for articles published in English from conception to July 2022 to identify retrospective cohort or database studies for inclusion. Studies must have included HPV+ patients with OPSCC who were treated with TORS. Outcomes must have included survival rates and recurrence rates. Two reviewers (BKW, FGD) independently performed study screening, data extraction, and risk of bias assessment. Meta-analysis of proportions and comparison of weighted proportions were performed in MedCalc 20.110.

Results: A total of 44 studies met inclusion criteria. In studies (n=902 patients) comparing TORS vs. non-surgical interventions (NS), primarily radiotherapy (RT), overall survival (OS) for TORS patients (94.7% [95% CI 92.5% to 96.6%]) was significantly higher than NS patients (91.2% [88.4% to 93.6%]) with a difference of 3.5% ([0.14% to 6.9%], p=0.0399). In other studies (n=3469 patients) comparing TORS vs. non-robotic surgery (NRS), OS for TORS patients was 88.8% [87.2% to 90.3%] while OS for NRS patients was 86.1% [79.6% to 91.5%] with a difference of 2.7% ([0.46% to 4.9%], p=0.0181). Fifteen studies with a total of 8,149 patients demonstrated an OS of 94.1% [91.7% to 96.1%], Disease Free Survival (DFS) 87.3% [85.6% to 88.9%], All Recurrence 10.6% [6.6% to 15.5%], Locoregional Recurrence 6.1% [3.0% to 10.2%], and Distant Metastatic Recurrence 7.0% [5.8% to 8.3%].

Conclusions: Use of TORS as the primary treatment modality for HPV+ OPSCC shows significantly improved survival outcomes compared to non-robotic surgery or non-surgery (primary RT).

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#5272

EFFECTIVE HPV VACCINATION EDUCATION FOR ORAL HEALTH PROFESSIONALS: OUTCOMES OF A QUALITATIVE EVALUATION

38 - Health education

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Background/Objectives: Given the increase in Human Papillomavirus (HPV) associated Head and Neck Cancer rates, discussing and advocating for the HPV vaccine is an opportunity for oral health providers. However, oral health providers need knowledge and practice to integrate such information into their dental patient counseling. Therefore, health education is needed for oral health providers to adopt recommending the HPV vaccine skillfully. This presentation reviews the results of a study examining an innovative health education training model using adult learning principles and health behavior change theory to increase recommendations of the HPV vaccine by oral health providers.

Methods: We designed a health education training model based on adult learning principles and health behavior change theory to increase knowledge, positive attitudes, and behaviors leading to recommending the HPV vaccine by hygienists, dental assistants, and dentists. Following 90 minutes of provider instruction, trained youth actors role-played an individual needing an HPV vaccine. Provider participants volunteered to practice demonstrated interviewing skills with a youth actor while their colleagues observed. Instructor lead feedback regarding the interview's strengths and opportunities for improvement were processed as a group. A qualitative evaluation study was conducted one-year post-training. Video-based, in-depth, open-ended interviews lasting approximately 30 minutes examined the effectiveness of the health educational model and changes in providers' knowledge, attitudes, and behaviors regarding recommending the HPV vaccine. This study was deemed exempt from the University of Minnesota IRB (Ethos Study ID STUDY00008406).

Results: Three dentists and nine dental assistants or dental hygienists participated in the interviews out of the sixty-one providers trained. Saturation was reached at twelve. Answers documented acceptance of the learning strategy and increased knowledge, more positive attitudes, and new behaviors regarding recommending the HPV vaccine. In particular, respondents noted role-play with youth actors as a highly effective learning methodolgy.

Conclusions: Oral health providers need intentionally designed health education and practice to affect their knowledge, attitudes, and behaviors regarding recommending the HPV vaccine. Providing essential information on HPV and the HPV vaccine, as well as the use of simulated patients of the age of those who are to be counseled for HPV vaccination in a dental visit, is a highly effective training model. This model results in greater knowledge of HPV and more positive attitudes toward recommending the HPV vaccine, as well as increased recommendations of the HPV vaccine by oral health providers.

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#4777

Evaluation of the attributable fraction and burden of HPV-related ORoPHaryngEal cAncerS in Greece-The ORPHEAS study

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Previous studies have reported that the attributable fraction (AF) of HPV-positive (HPV+) oropharyngeal cancer (OPC) is low in Southern compared to Northern European countries (~9-24% versus ~50%). Robust epidemiological data investigating the association of HPV with OPC are lacking in Europe. Here, we present the interim outcomes of the ORPHEAS study, assessing the AF of HPV+ OPCs in Greece.

Methods: ORPHEAS is an ongoing observational, retrospective, cross-sectional study with prospective recruitment, aiming to enroll 150 patients (pts) from 9 reference hospitals in Greece. Eligible are pts diagnosed with OPC as per medical records from Q1 2017 to Q3 2022 who have a high-quality treatment-naïve tumor sample available. The primary endpoint is the AF of HPV+ OPCs among all OPCs, as assessed by both p16 immunochemistry and HPV DNA PCR-ELISA-DEA test (using SPF10 primers) by a central laboratory. Other endpoints include the description of pt characteristics at OPC diagnosis, overall and for newly diagnosed pts (i.e., diagnosed with OPC 2 months before study entry), and the assessment of HPV types for pts with HPV+ OPC with LiPA strips. This interim analysis included the first 74 OPC pts.

Results: Most pts were males (57, 77.0%). The overall pt median age at OPC diagnosis was 59.3 years; 25 (33.8%) and 26 (35.1%) pts were former and current smokers, respectively. The most common tumor anatomical sites were the tonsils (39 pts, 52.7%) and the base of the tongue (22 pts, 29.7%); the median tumor size was 3.0 cm. Of pts with available tumor staging as per TNM 8th Edition (61 pts), 26.2%, 23.0%, 19.7% and, 31.1% were stage I, II, III, and IV, respectively. Among pts with available HPV status as per central laboratory (69 pts), the AF of HPV+ OPCs (combined positivity DNA/p16) was 59.4% (41/69 pts; 95% confidence interval 46.9-71.1). HPV 16 was detected in 95.1% (39/41) of HPV+ OPC samples. HPV+ pts compared to HPV- pts were younger (median age 57.0 and 65.0 years, respectively; p=0.116), less frequently ever smokers (7.7% and 35.1%, respectively; p=0.021) and more frequently had tumor in the tonsils (68.3% and 32.1%, respectively; p=0.003); males were 33 (80.5%) and 20 (71.4%; p=0.381) pts, respectively.

Conclusions: This interim analysis of the ORPHEAS study showed a high AF of HPV+ OPCs in Greece (~60.0%), with HPV 16 being the main causative type. HPV+ pts were more commonly male, younger and never smokers than HPV− pts. Since a substantial number of OPC cases are preventable, according to these preliminary results, it is highlighted a potential benefit of recently introduced gender neutral HPV vaccination in Greece.