EUROGIN 2022 ABSTRACTS

MAIN CONGRESS PROGRAM

FDW Part 1 Cervix - B) HPV primary screening of CIN3-ADC in situ: new insights and long-term performance

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#3959

Epigenetics and methylation markers for CIN3+ detection

15 - Molecular markers

Background/Objectives: Disruption of DNA methylation patterns is one of the hallmarks of cancer, including high-risk human papillomavirus (hrHPV)-driven anogenital cancers. Several hyper-methylated cellular genes have been found associated with carcinogenesis of the uterine cervix or other anogenital sites. 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: Using targeted and genome wide approaches various host cell genes that become methylated during HPV-induced carcinogenesis have been defined. Selected methylation markers were tested and validated in HPV-positive cervical scrapes and self-samples for CIN2/3 and cancer detection.

Results: Methylation markers detect virtually all cervical cancers. In CIN2/3 with varying cancer risks, distinct methylation patterns were seen. Our data indicate that so-called advanced CIN lesions display a cancer-like methylation-high pattern and have a high short-term risk of progression to cancer.

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.

SS02- Is HPV genotyping transforming primary HPV screening?

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#3943

Role of HPV Genotyping in Refining Cervical Screening

10 - HPV screening

Background/Objectives: See accompanying email for this

Methods: as above

Results: as above

Conclusions: as above

SS04- HPV and anal cancer diseases - screening

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#3968

Incidence and clearance of anal human papillomavirus infection in 13,928 individuals, according to HIV status, sex, and male sexuality: a collaborative pooled analysis of 26 longitudinal studies

03 - Epidemiology and natural history

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Background/Objectives: Understanding natural history of anal high-risk human papillomavirus (hrHPV) is key for designing anal cancer prevention programs, but has not been systematically characterised.

Methods: We reanalysed data from 26 studies with 13,928 individuals in six risk groups defined by HIV status, sex, and male sexuality: men who have sex with men (MSM) living with HIV (LWH) [MSMLWH], HIV-negative MSM, women LWH (WLWH), HIV-negative women, men who have sex with women (MSW) LWH (MSWLWH) and HIV-negative MSW. Markov models were used to estimate incidence and clearance of 13 hrHPV types and their determinants.

Results: HPV16 showed highest incidence/clearance-ratio of hrHPV types. MSMLWH had highest hrHPV incidence (e.g. 14·7% newly HPV16-infected within 2 years), then HIV-negative MSM (7·1%), WLWH (6·5%), HIV-negative women (2·9%), MSWLWH (1·3%), and HIV-negative MSW (0·6%). Determinants of HPV16 incidence included HIV-positivity and number of sexual partners for MSM and women, as well as anal sex for MSM but not for women. Anal HPV16 clearance was significantly lower for people LWH (PLWH), and significantly lower for prevalent than incident infections. Among MSM, increasing age was a strong predictor of persistence of prevalent, but not incident, HPV16 infections.

Conclusions: This robust and unifying pooled analysis of anal hrHPV natural history will underpin designing and predictions of impact of HPV-vaccination and HPV-based screening programs on anal cancer prevention, particularly in MSM and PLWH. Importantly, it establishes the evidence for the concept of differential carcinogenic potential of longstanding versus more recent anal hrHPV infection.

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#4003

Suitability of clinician-performed Digital Anal Rectal Exams for detection of HPV-associated palpable lesions

16 - Screening methods

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Background/Objectives: The Digital Anal Rectal Examination (DARE) was fullly described for the first time in 2018 by the International Anal Neoplasia Society. In July 2021, it was recommended by the United States Centers for Disease Control and Prevention for anal cancer screening in persons with HIV (PWH) and in HIV-negative gay and bisexual men. For people in areas with no high-resolution anoscopy infrastructure, DARE may be the only option for detection of anal cancer. Yet to date, there have been few reported data on the suitability and performance of DARE for anal cancer screening. Our objective was to describe the use of DARE in the Prevent Anal Cancer (PAC) studies at baseline.

Methods: Gay and bisexual cis-gendered men who were PWH or HIV-negative, and transgender persons who have sex with men, aged ≥ 25 years, were recruited into the PAC studies in the US from Chicago, Houston, and Milwaukee. Data from the first 560 participants to receive a DARE were analyzed. The performance of 16 PAC Study clinicians were described including DARE adequacy, length of time for DARE, and referral patterns. Lesion findings by DARE were stratified by HIV status and included lesion size, type, and location.

Results: Clinicians were 6 medical doctors (MD), 6 advanced practice nurses (APN), and 4 registered nurses (RN). Median age of enrolled participants was 42 years (range 25-80 years) and 31.0% were PWH. Eleven percent of participants reported a DARE in the prior year. Clinicians reported adequate examination of the perianus and anal canal in 556/560 participants. Median time to complete DARE was 1 minute and did not differ by presence of an abnormality. A total of 285 anal canal and perianal lesions among 211 (37.7%) participants were annotated with a higher proportion of lesions among PWH. Thirty persons had lesions at both anal canal and perianus. Of 79 participants with masses, focal areas of thickening or granularity, or linear lesions in the anal canal, 21 (26.5%) were labeled as "suspicious" or as condyloma. Of 162 participants with perianal lesions, 14 (8.6%) were labeled as "suspicious" or as condyloma. The median size of anal canal and perianal lesions was 3 mm (range 1-40 mm) and 3 mm (range 1-30 mm), respectively, with lesion size largest in Milwaukee. A total of 7.1% of participants were referred for additional care with PWH more likely to get referred (p=0.02). Compared to MDs, RNs were more likely to report anal canal and perianal abnormalities (p=0.003 and p=0.002, respectively) and more likely to make a referral (p=0.04). In a subset of 125 participants, < 5% reported the DARE as "quite a bit" or "very" embarrassing, uncomfortable, or anxiety producing.

Conclusions: Clinicians were able to recognize and describe anal canal and perianal lesions efficiently. The proportion of participants referred was low; however, RNs documented more lesions and referred participants to additional care more often than physicians. Referral patterns and variance in lesion size indicate the importance of DARE-specific training for HCPs. NCT03489707 and NCT04090060.

References: Hillman RJ, Berry-Lawhorn JM, Ong JJ, et al. International Anal Neoplasia Society guidelines for the practice of digital anal rectal examination. J Low Genit Tract Dis 2019;23:138-46. doi: 10.1097/lgt.0000000000000458

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#3978

Disparities in uptake of anal cancer screening

28 - Anal neoplasia

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Background/Objectives: Implementation of anal cancer screening has the potential to significantly reduce the burden of anal cancer among people living with HIV. It is imperative that facilitators to screening are identified to ensure high levels of participation and equitable access to care. Using data from an ethno-racially diverse cohort of people living with HIV, our objective was to assess HPV-related knowledge, past participation in and beliefs regarding anal cancer screening and identify factors associated with willingness to participate in screening.

Methods: Results will be presented from cross-sectional questionnaires that were developed using the Theory of Planned Behavior to examine factors such as knowledge and beliefs that influence participation in HPV prevention strategies. The questionnaires were administered to men and women living with HIV in a multi-site HIV clinical cohort in Canada. These results will be presented in concert with emerging literature to discuss potential disparities in anal cancer screening participation as international guidelines are being considered.

Results: Racialized men were less likely to report undergoing anal cancer screening, regardless of sexual orientation, such that even among gay, bisexual and other men who have sex with men who are prioritized for preventive screening, there were racial inequities. This disparity in uptake of anal cancer screening occurred despite universal access to medically necessary services in our setting. However, the vast majority of men were willing to undergo screening in the future. Men generally had positive beliefs regarding the screening process, which were associated with increasing willingness to be screened, as posited by the Theory of Planned Behavior. Heterosexual men and racialized men reported lower willingness to be screened, though willingness was still very high among these men. Results on knowledge and willingness to undergo anal cancer screening among women living with HIV will also be discussed.

Conclusions: Observed disparities in knowledge, uptake, and willingness to undergo screening are notable, suggesting future disparities in anal cancer screening and outcomes. Accordingly, we believe these data are timely to inform development and implementation of anal cancer screening guidelines and community-led initiatives to encourage equitable attendance.

References: PLEASE NOTE: This abstract is submitted in reference to an invited speaker presentation -Scientific Session 4: Anal Cancer Screening / Chaired by A. Nyitray (USA), L. Abramowitz (France) / April 10 / 13:30 - 15:00 / Title: Disparities in uptake of anal cancer screening ACKNOWLEDGEMENTS: These data arise from a large anal cancer screening study among men living with HIV in Canada, the HPV-SAVE study (PIs: Troy Grennan & Irving Salit) and a study among women living with HIV (PIs: Ann Burchell & Jennifer Gillis). I thank all co-investigators of these studies (HPV-SAVE: Ron Rosenes, Jason Brunetta, Owen McEwen, Ann Burchell, Rupert Kaul, Paul MacPherson, Janet Raboud, Anita Rachlis, Alberto Severini, Darrell Tan, Jill Tinmouth, Daniel Grace, Joel Palefsky; HPV Prevention in WLHIV: Joanne Lindsay, Mona Loutfy, Claire Kendall, Janet Raboud, Anita Rachlis, Beth Rachlis, Anita Benoit, Mark Yudin, Gina Ogilvie, Abigail Kroch, Ramandip Grewal, Anna Yeung). Altogether, we gratefully acknowledge and thank the Ontario HIV Treatment Network (OHTN) Cohort Study participants, OHTN clinical and research staff, and Governance Committee members.

WS02 - Prevention of anal cancer post-ANCHOR

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#3977

Should screening for and treating anal HSIL be included in standard of care guidelines? What additional information is needed?

36 - Economics and modelling

Background/Objectives: New data from the Anal Cancer HSIL Outcomes Research (ANCHOR) study (indicating that anal HSIL treatment results in a 57% reduction in anal cancer incidence compared to active monitoring among HIV-infected persons with HSIL) provides a foundational benchmark to answer several unaddressed questions, including whether screening for and treating anal HSIL could be included in the standard of care guidelines and what additional data are critical to improve our understanding of population-level harms and benefits, necessary to inform optimal screening and treatment algorithms.

Methods: This talk will be guided by our ongoing efforts to synthesize a comprehensive mathematical modeling framework (Simulation Model of Anal Cancer: SMAC) of HIV, HPV, and anal precancer/cancer natural history that aims to determine effective and cost-effective age-specific anal cancer screening (for prevention and early detection) and anal HSIL treatment algorithms.

Results: Designed using empirical data and integrating anal HSIL treatment efficacy (57% reduction in cancer incidence) into the mathematical modeling (SMAC) framework, this talk aims to cover several pragmatic questions, including (1) downstream (i.e., extrapolation beyond-trial follow-up) implications of active monitoring versus anal HSIL treatment (in comparison with the disease natural history) and (2) key real-world attributes related to human behavior and access to care (e.g., treatment uptake and compliance) that will impact anal cancer prevention and/or early detection and further translation of these outcomes into survival benefits. In addition, the talk will also cover key questions, including (3) important disease natural history (e.g., progression/regression) and anal HSIL treatment-related aspects that will likely drive outcomes of screening and treatment, in terms of harms/benefits, stage-shift protection, quality of life, and downstream impact on survival, and (4) current uncertainties and additional data that is necessary to inform age-specific risk-based screening algorithms guided by the principle of equal risk/equal management.

Conclusions: Evidence-based optimal anal cancer screening guidelines are needed, informed by the determination of optimal use of screening (in terms of screening initiation/frequency/termination) for and treatment of anal HSIL. It is also crucial that currently scarce screening resources be directed to key risk groups to optimize screening use and ensure risk-targeted equitable prevention/early detection. This talk suggests a framework for integrating anal HSIL treatment efficacy into the anal cancer control continuum and highlights current uncertainties and the importance of addressing them to improve anal cancer prevention/early detection among key risk groups.

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#3954

Methylation analysis of anal cancer and pre-cancerous lesions- implications for cancer risk stratification of anal HSIL

28 - Anal neoplasia

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Background/Objectives: High-grade anal intraepithelial neoplasia (HGAIN; AIN2/3) is highly prevalent in HIV+ men, but only a minority will progress towards cancer. Since the risk of progression cannot be established, current screening options result in substantial over-referral and overtreatment. Therefore risk stratification of HGAIN using biomarkers is needed.

Methods: Host cell DNA methylation markers for detection of HGAIN and anal cancer were evaluated in a cross-sectional series of 148 anal tissue samples of HIV+ men using quantitative methylation-specific-PCR. The best performing markers were validated in a large, independent cross-sectional series of 345 HIV+ samples and also evaluated in a cross-sectional series of 176 samples of HIV-negative women and men. Accuracy for detection of AIN3 and cancer was determined by univariable and multivariable logistic regression analysis, followed by leave-one-out-cross-validation. The association with cancer progression was assessed in a longitudinal series of ten anal cancer cases with preceding HGAIN at similar anatomic locations.

Results: In all series of anal biopsies tested methylation marker levels increased with increasing severity of disease ($p<0.05$). A high resemblance was found between all patient groups. Histopathologically similar HGAIN revealed a heterogeneous methylation pattern, a subset resembling cancer. In HIV+ MSM a three-marker panel ASCL1, SST, ZNF582 was most accurate (AUC=0.89) in distinguishing AIN3 and cancer from controls, not missing cancers. AIN3+ detection using these markers in HIV-negative women and men was comparable (AUC=0.85). In the longitudinal series, all HGAIN preceding cancer displayed high methylation levels similar to cancers.

Conclusions: We identified and validated methylation markers for the detection of anal (pre-)cancer in HIV+MSM. Accurate AIN3+ detection was confirmed in HIV-negative patients. High methylation levels were associated with progression to cancer. Therefore, these methylation markers provide a promising cancer risk stratification tool for all risk groups of anal cancer. Methylation testing can identify HGAIN in need of treatment and prevent overtreatment of HGAIN with a low cancer risk. A prospective clinical validation study has recently been initiated.

References: van der Zee, RP, Richel, O, van Noesel, CJM, Novianti, PW, Ciocanea-Teodorescu, I, van Splunter, AP, Duin, S, van den Berk, GEL, Meijer, CJLM, Quint, WGV, de Vries, HJC, Prins, JM & Steenbergen, RDM 2019, 'Host Cell Deoxyribonucleic Acid Methylation Markers for the Detection of High-grade Anal Intraepithelial Neoplasia and Anal Cancer', Clinical Infectious Diseases, vol. 68, no. 7, pp. 1110-1117 van der Zee, RP, Richel, O, van Noesel, CJM, Ciocănea-Teodorescu, I, van Splunter, AP, Ter Braak, TJ, Nathan, M, Cuming, T, Sheaff, M, Kreuter, A, Meijer, CJLM, Quint, WGV, de Vries, HJC, Prins, JM & Steenbergen, RDM 2021, 'Cancer risk stratification of anal intraepithelial neoplasia in HIV-positive men by validated methylation markers associated with progression to cancer', Clinical infectious Diseases. 72, 12, p. 2154-2163 van der Zee, RP, van Noesel, CJM, Martin, I, Ter Braak, TJ, Heideman, DAM, de Vries, HJC, Prins, JM & Steenbergen, RDM 2021, 'DNA methylation markers have universal prognostic value for anal cancer risk in HIV-negative and HIV-positive individuals', Molecular oncology. Nov;15(11):3024-3036. van der Zee, R. P., Meijer, C. J. L. M., Cuming, T., Kreuter, A., van de Sandt, M. M., Quint, W. G. V., de Vries, H. J. C., Prins, J. M. & Steenbergen, R. D. M. 2021, Characterisation of anal intraepithelial neoplasia and anal cancer in HIV-positive men by immunohistochemical markers p16, Ki-67, HPV-E4 and DNA methylation markers, Int J. of Cancer. 149, 10, p. 1833-1844

FDW Part 2 - New insights in high-grade intraepithelial neoplasia of anus, vulva and oropharynx

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#3963

Cancer risk and biomarkers in high-grade vulvar intraepithelial neoplasia

15 - Molecular markers

Background/Objectives: Cancer risk and biomarkers in high-grade vulvar intraepithelial neoplasia High-grade vulvar intraepithelial neoplasia (HG-VIN), the precursor of vulvar carcinoma, can be divided into HPV-associated HSIL and HPV-independent and lichen sclerosus (LS)-associated dVIN. HSIL is much more commonly diagnosed than dVIN and the cancer risk is relatively low. In contrast, timely and accurate diagnosis of dVIN is difficult, while the cancer risk is high. The use of immunohistochemical biomarkers and HPV assays can improve the identification of HSIL and dVIN. Host cell DNA methylation markers can identify vulvar lesions with a high cancer risk, which are promising for refining diagnostics and tailored management in affected women.

Methods:

Results:

Conclusions:

References:

SS05- The utility of urine for improved cervical cancer prevention

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#3724

HPV TESTING OF SELF-COLLECTED FIRST-VOID URINE SAMPLES: COMPARISON OF PERFORMANCE USING DEVICES COLLECTING DIFFERENT URINE VOLUMES

13 - Self-sampling

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Background/Objectives: HPV testing of self-collected samples has been demonstrated to be a valid alternative to reach women reluctant to undergo clinician-based cervical cancer screening. First-void urine (FVU) has been recently proposed to be a less invasive sample with a similar clinical accuracy to cervical sample in detecting high-grade cervical intraepithelial neoplasia. Colli-Pee® device allows standardized collection of different volumes of FVU captured in a collector tube prefilled with a preservation solution. The aim of the study was to evaluate the accuracy of HPV testing on urine self-samples using two different devices able to collect different volumes of FVU (20ml and 10ml) as compared to cervical samples (gold standard) in women referred to colposcopy.

Methods: Clinician-collected cervical (L-shaped Endo/Esocervical FloqSwab®, Copan) and FVU samples (Colli-Pee®, Novosanis), were obtained from 90 women attending the Colposcopy Clinic, San Gerardo Hospital (Monza, Italy). Two different devices using volume variants have been tested: 45 women collected FVU using the 10mL and 45 women using the 20mL Colli-Pee®device. All samples were extracted using MicroLab Nimbus starting from 200 µl of sample and HPV detection carried out using AnyplexII HPV28 (Seegene). Concordance in HPV detection between sample types was determined using Cohen's Kappa value (k).

Results: 44% (20/45) and 51% (23/45) of women that used respectively the 10ml and the 20ml Colli-Pee® devices resulted positive in clinician-collected cervical sample for one or more hrHPV infections. A good concordance for hrHPV was observed between clinician-collected cervical and urine samples collected using both devices (82.2% total agreements for 10mL and 20mL, respectively). In particular HPV16 and HPV18, responsible for over 70% of cervical cancer cases, showed high agreement rates between cervical and urine samples collected using both devices (10 mL Colli-Pee®: HPV16: k= 0.897 HPV18 k=1.000; 20 mL Colli-Pee®: HPV16: k=1.000 HPV18: k=1.000).

Conclusions: These preliminary data demonstrate promising results for the use of both urine collecting devices in cervical cancer screening. The high concordance rate for hrHPV detection, including the lower volume collection device, if confirmed by larger number of tested samples, would suggest the possibility and feasibility of performing FVU home-collection in screening programs, allowing increased and safer participation of women to cervical cancer screening even during COVID-19 pandemic.

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#3938

URINARY HPV DNA TESTING AS A TOOL FOR CERVICAL CANCER SCREENING IN FRENCH WOMEN

13 - Self-sampling

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Background/Objectives: Despite population-based campaigns including invitation letters sent to women recommending them to contact a physician to take a cervical sample, cervical cancer screening coverage remains moderate (~60%) in France. We conducted the CapU1 study in France (Maine-et-Loire department) on women who did not undergo a Pap-smear during the last three years. This study demonstrated that urine self-sampling increases patient compliance and can be relevant to detect high grade cervical lesions (1). Because of these promising results and in order to extend the screening coverage, we led a third study named CapU3 (2). This study sent approximately 13 000 urine collection kits to women living in the Department of Maine-et-Loire, aged 35-65 years, who did not have screening record since seven years ago or longer. The participation rate was 15.4% and good gynecological follow-up after a positive urinary HPV testing was observed (92.1 %). However, the CapU3 trial did not include a comparison arm impeding to demonstrate evidence of comparative efficacy. Since 2019, the French health authority specifies that vaginal self-sampling is possible for women who are not regularly screened. The collection of a urine specimen is less invasive for women reluctant to undergo gynaecological sampling (cervical sampling or vaginal self-sampling) and may generate higher participation rates. Consequently, the aim of the CapU4 study is to evaluate the effectiveness of two experimental invitation strategies (urine or vaginal self-sampling) to reach under-screened populations and compare them to the current invitation strategy in two rural medically under-served departments, in France, with low screening coverage.

Methods: The CapU4 study is a randomized controlled trial with three arms. The target population (15 000 women) includes women aged 30-65 years, living in two rural departments with low medical density, who had no screening test recorded since more than four years and who did not respond to an invitation letter within twelve months before. A team of psychologists will investigate attitudes and experiences by semi-structured/focus-group interviews with voluntary CapU4 participants and with health professionals.

Results: This study, funded from the French National Institute, will begin in February 2022.

Conclusions: The Capu4 study will for the first time compare directly two experimental invitation strategies (offering self-sampling of vaginal specimens or collection of first-void urine) with the current procedure including traditional reminder letters. CapU4 will identify effective strategies to reach women not responding to current screening invitations and will generate information about acceptance of self-sampling among women and health professionals.

References: 1. Ducancelle A, Reiser J, Pivert A, Le Guillou-Guillemette H, Le Duc-Banaszuk AS, Lunel-Fabiani F. Home-based urinary HPV DNA testing in women who do not attend cervical cancer screening clinics. J Infect. 2015;71(3):377-84. 2. Lefeuvre C, Pivert A, Guillou-Guillemette HL, Lunel-Fabiani F, Veillon P, Le Duc-Banaszuk A-S, et al. Urinary HPV DNA testing as a tool for cervical cancer screening in women who are reluctant to have a Pap smear in France. J Infect. 2020;81(2):248-54.

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#4005

Detection of Cervical Cancer and Cervical Intraepithelial Neoplasia by hrHPV Analysis and DNA Methylation Analysis in Urine and Preferences for Cervical Cancer Screening Methods

18 - Methylation

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Background/Objectives: Offering urine as sampling method for cervical cancer screening may lead to increased attendance rates. Therefore, we aimed to determine the detection rate of cervical cancer and high-grade cervical intraepithelial neoplasia (CIN2/3) in urine and cervical (self)samples by analyzing the presence of high-risk human papillomavirus (hrHPV) and the levels of DNA methylation markers. Secondly, we evaluated preferences for different sample types for future cervical cancer screening in patients planned for a large loop excision of the transformation zone (LLETZ).

Methods: A total of 587 urine samples, cervicovaginal self-samples and clinician-taken cervical scrapes were included from 113 women with cervical cancer, 92 women with CIN2/3, and 64 controls. Samples were tested for hrHPV DNA and five methylation markers (ASCL1, GHSR, LHX8, SST, ZIC1). Using univariate and multivariate logistic regression and leave-one-out cross-validation, the methylation marker performance for detection of CIN3 and cervical cancer (CIN3+) in urine was determined. The agreement between samples was calculated using Cohen's kappa statistics and the Spearman correlation coefficients. In addition, 140 women, who were planned for LLETZ, filled in a questionnaire about their experiences with urine collection and cervicovaginal self-sampling and about their preferences for the sampling method of future cervical cancer screening.

Results: HrHPV presence was high in all sample types, 79% to 92%. All five methylation marker levels rose significantly with increasing severity of disease. The optimal marker panel (ASCL1/LHX8) resulted in an AUC of 0.84 for CIN3+ detection in urine, corresponding to an 86% sensitivity at a 70% predefined specificity. At this threshold 96% (109/113) of cervical cancers, 68% (46/64) of CIN3 and 58% (14/24) of CIN2 were detected. A strong agreement for HPV16/18 genotyping and a fair to strong correlation for methylation markers was observed between paired samples. Regarding patient's experiences with sample collection, patients considered urine collection compared to cervicovaginal self-samples as more acceptable ($p<0.001$) and to provide more reliable results ($p<0.001$). For future cervical cancer screening the majority of patients preferred urine collection (28%). Other preferred sampling types were: clinician-taken cervical scrape (23%); equal preference for urine collection, clinician-taken cervical scrape and cervicovaginal self-sampling equally (21%); cervicovaginal self-sampling (14%); equal preference for urine collection and cervicovaginal self-sampling (9%); equal preference for urine collection and clinician-taken cervical scrape (4%); missing (1%).

Conclusions: HrHPV DNA and DNA methylation testing in urine offers a promising solution to detect cervical cancer and CIN2/3 lesions. The majority of the patients preferred urine collection for future cervical cancer screening. Urine collection followed by molecular analysis may provide a solution to reach non-attendees of cervical cancer screening.

References: van den Helder, R., Steenbergen, R. D., van Splunter, A. P., Mom, C. H., Tjiong, M. Y., Martin, I., Rosier-van Dunné, F. M. F., van der Avoort, I. A. M., Bleeker, M. C. G., & van Trommel, N. E. (2022). HPV AND DNA METHYLATION TESTING IN URINE FOR CERVICAL INTRAEPITHELIAL NEOPLASIA AND CERVICAL CANCER DETECTION. Clinical cancer research: an official journal of the American Association for Cancer Research. Schaafsma, M., van den Helder, R., Bleeker, M. C. G., Rosier-van Dunné, F. M. F., van der Avoort, I. A. M., Steenbergen, R. D., & van Trommel, N. E. (2022). Experiences and preferences towards collecting a urine and cervicovaginal self-sample among women attending a colposcopy clinic. Preventive medicine reports, 101749.

CS01- New strategies for monitoring disease in the test of cure population

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#3975

TYPE SPECIFIC PERSISTENCE IN THE TEST OF CURE POPULATION AND IMPLICATIONS FOR MANAGEMENT.

14 - Genotyping

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Background/Objectives: Women diagnosed with cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and treated by excisional procedures remain at high risk for recurrence over time. "Treatment failure" has been reported in up to 23% of women within two years after treatment. The aim of this study was to investigate the impact of HPV same genotype persistence on CIN2+ recurrence. As secondary outcomes, we evaluated the impact of multiple genotypes and of specific HR genotype, especially HPV 16/18, on recurrence risk.

Methods: A prospective cohort observational study was carried out at the European Institute of Oncology, Milan, Italy, from December 2006 to December 2014. HPV test was performed at the time of treatment ("baseline") and as "test-of-cure" at first follow-up visit planned at 6 ± 3 months after treatment. A ThinPrep PreservCyt (Hologic, Inc, Bedford, MA, USA) cervical sample was collected in all patients to perform Hybrid Capture 2 HR-HPV Test (HC2; Qiagen, Gaithersburg, MD, USA) and Linear Array HPV Genotyping Test (Roche Diagnostics, Pleasanton, CA, USA), in case of positive HC2 test. Two-year cumulative incidences for relapse were estimated and compared by the Gray's test.

Results: A total of 408 women surgically treated by excisional procedure for pre-neoplastic and neoplastic cervical lesions were enrolled. Overall, 96 (23.5%) patients were persistent for at least one genotype at three to nine months from baseline and 21 (5.1%) patients relapsed. Whereas histological grade, glandular crypt involvement, and margin status are not significantly related with treatment failure, HPV same genotype persistence has 30-fold increased odds of developing relapse ($p < 0.001$). The two-year cumulative relapse incidence was higher in HPV persistent patients compared to not-persistent (CIF = 27.6%, 95% CI: 16.2-40.2% versus CIF = 1.7%, 95% CI: 0.3-5.8%, $p < 0.001$), in women with persistent multiple infections (CIF = 27.2%, 95% CI: 7.3-52.3%, $p < 0.001$), and with the persistence of at least one genotype between 16 and 18, irrespective of the presence of other HR genotypes (CIF = 32.7%, 95% CI: 17.9-48.3%, $p < 0.001$), but not significantly different from women positive for single infections or any other HR genotype, but not for 16 and 18.

Conclusions: The risk of CIN2+ recurrence should not be underestimated when same HPV genotype infection persists after treatment, even in women with negative resection margins. HPV genotyping as "test-of-cure" enables a personalized risk-based management, by identifying women at higher risk of relapse who need intensive follow-up and avoiding risk of over-treatment in women with new HPV genotype infection after surgery.

References: Iacobone AD, Radice D, Sandri MT, et al. Human Papillomavirus Same Genotype Persistence and Risk of Cervical Intraepithelial Neoplasia2+ Recurrence. Cancers (Basel). 2021;13:3664. Acknowledgments: This work was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5 × 1000 funds.

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#3981

OPTIMAL MANAGEMENT OF OLDER WOMEN TREATED FOR CIN: BALANCING THE RISKS AND BENEFITS

24 - Risk management

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Background/Objectives: Women having been treated for CIN are still confronted with increased risk of cervical cancer, particularly at older ages exiting routine screening program1. The management for this group is challenging: morphological assessment and HPV testing performance may be hindered due to atrophy of cervix, and colposcopy evaluation can be unsatisfied due to the complication of cervical stenosis after CIN treatment. We aim to identify the challenges and discuss potential superior managements.

Methods: We used the Swedish National Cervical Screening Registry to examine the positivity proportion of HPV and cytology among women exiting screening program who had had history of CIN2+ (great majority of them were treated). When assessing HPV with partial genotyping result, 455 tests at ages 65-70 in Stockholm region during 2013-2020 with history of CIN2+ were included. When assessing cytology positivity, 20,635 tests at ages 65-70 in entire Sweden during 1981-2020 with history of CIN2+ were included.

Results: Among women aged 65-70 who had had history of CIN2+, 20% were tested positive for high-risk HPV, and 22% of the positive tests were HPV 16 or 18. The corresponding HPV positivity in general Swedish women population at ages 56-64 was around 8%, and 25% of the positive tests were HPV 16 or 18. On the other hand, only 9% of women aged 65-70 with history of CIN2+ were tested positive for cytology (ASCUS+). In a catch-up screening project, 566 women aged 65-70 who had had high-grade abnormality since age 50 without sufficient follow-up was targeted for self-sampling of HPV. Among 8 women who participated, tested high-risk HPV positive and participated in follow-up colposcopy, 4 had cervical stenosis thus were insufficient for histopathological diagnosis.

Conclusions: Our data implies that, HPV-primary testing may outperform cytology among older women exiting screening program with history of CIN2+. However, triage tests of either cytology or HPV genotyping are expected to be suboptimal. Moreover, colposcopy and biopsy for histopathology assessment are particularly challenging due to high prevalence of cervical stenosis. We are quantifying the effectiveness of current management strategies, hoping to facilitate the discussion about whether more aggressive treatment, e.g. hysterectomy, is necessary for certain groups. We also plan to explore whether other biomarkers, e.g. DNA methylation, may perform better on risk stratification for older women with CIN history.

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MSS 01.A - Covid-19 and HPV vaccination

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#3997

HPV vaccination and COVID, Europe

06 - HPV prophylactic vaccines

Background/Objectives: Human papillomavirus (HPV) is the commonest sexually transmitted virus worldwide, with first infection typically occurring soon after sexual debut. HPV-related diseases cause substantial morbidity and mortality globally [i]. Overall, 2.2 million new cancer cases were attributable to infections in 2018, representing 13% of all cancer cases (excluding non-melanoma skin cancers), with HPV counting for 690 000 new cases (ASIR 8·0 cases per 100 000 person-years), predominantly cervix uteri carcinoma 1. In Europe, cervical cancer ranks as the 9th most frequent cancer among women and the 2nd most common female cancer deaths in women aged 15 to 44 years [ii]. Cervical cancer is preventable and curable, as long as it is detected early and managed effectively.

Methods: In May 2018, the WHO Director-General announced a global call for action to eliminate cervical cancer. In August 2020 the World Health Assembly adopted the Global Strategy for cervical cancer elimination with the "90-70-90 Approach". This global strategy was promptly implemented by the European CanCer Organisation in December 2019 and by the European Union with Europe's Beating Cancer Plan of February 3, 2021, to accelerate the elimination of cervical cancer [ii], [iii].

Results: HPV vaccination is most effective if provided to both sexes. However, most countries in Europe do not currently vaccinate boys. HPV vaccination uptake also remains low in some countries. As of January 2020, in the World Health Organization European Region (WHO/ER) national recommendations for HPVv exist in 46/53 (87%) countries, of which 38 (83%), 2 (4%), and 6 (13%) countries provided full, partial, or no funding, respectively, for the primary cohort [i]. Fully or partially funded HPVv was provided for girls only in 25/53 (47%) countries and for both boys and girls in 15/53 (28%) countries and 30/53 (57%) WHO/ER countries reported VCRs. Monitored VCRs ranged from 4.3% to 99%. Of the 25 countries reporting a monitored VCR following at least two doses of HPVv, 24 (80%) pertained to a primary cohort of girls and 10/24 (42%) reported a high VCR (i.e. ≥71%), 6/24 (25%) reported a moderate VCR (i.e. 51-70%), 6/24 (25%) reported a low VCR (i.e. 31-50%), and 3/24 (13%) had a very low VCR (≤30%). Only Portugal exceeded its target for the primary cohort. Just four countries with a GNV program reported a monitored VCR for boys, which in all cases was categorized as either low (Austria) or very low (Czech Republic, Italy, and Switzerland). The COVID-19 pandemic has significantly disrupted HPV vaccination and screening programmes across Europe.

Conclusions: The Region as a whole experienced a smaller decline for routine immunization coverages during 2020 than all other regions of the world, but this decrease masks large variations among countries, with larger declines in some countries, and a lack of reported data from some countries where COVID-19 disruptions have also affected capacity to collect and report routine immunization coverage data [ii].Additional efforts are required to ensure HPVv NIPs are fully funded and high VCRs maintained, contrasting discrepancies in vaccination coverage to enable elimination of all HPV-related cancers. Now is the time for decisive action to create an HPV-cancer-free future for men and women across Europe.

References: [1] Catherine de Martel, Damien Georges, Freddie Bray, Jacques Ferlay, Gary M Clifford. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020;8: e180-90. [1] Cervical Cancer Prevention Policy Atlas 2020. 22/01/2020. Available at: Cervical Cancer Prevention Policy Atlas 2020 | EPF (epfweb.org). [1] World Health Organization. Cervical Cancer Elimination Initiative. Available at: Cervical Cancer Elimination Initiative (who.int) [1] Peter Baker, Daniel Kelly, Rui Medeiros, Mike Morrissey, Richard Price. Eliminating HPV-caused cancers in Europe: Achieving the possible. Journal of Cancer Policy 28 (2021) 100280. [1] European Public Health Alliance. Europe's Beating Cancer Plan: the path towards cervical cancer elimination. Jul 7, 2021. Available at: Europe's Beating Cancer Plan: the path towards cervical cancer elimination - EPHA. [1] Paolo Bonanni, Pascaline Faivre, Pier Luigi Lopalco, Elmar A. Joura, Tobias Bergroth, Stefan Varga, Nathalie Gemayel & Rosybel Drury (2020): The status of human papillomavirus vaccination recommendation, funding, and coverage in WHO Europe countries (2018-2019), Expert Review of Vaccines, DOI: 10.1080/14760584.2020.1858057. [1] World Health Organization/Europe. Varied impact of COVID-19 on routine immunization in the European Region. 16-07-2021. Available at: WHO/Europe | Vaccines and immunization - Varied impact of COVID-19 on routine immunization in the European Region. [1] European Parliament resolution of 16 February 2022 on strengthening Europe in the fight against cancer - towards a comprehensive and coordinated strategy. Texts adopted - Strengthening Europe in the fight against cancer - Wednesday, 16 February 2022 (europa.eu).

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#3973

HPV VACCINATION IN THE UNITED STATES: EFFECTS OF THE COVID-19 PANDEMIC, 2020-22

40 - Public health

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Background/Objectives: The United States declared a national emergency in response to the COVID-19 pandemic on March 13, 2020. Stay-at-home orders and staffing shortages resulted in disruptions in preventive health care services. In the United States, routine HPV vaccination is recommended at age 11-12 years with catch-up through age 26. Most HPV vaccinations are provided in primary care settings and about 50% of adolescents are eligible for public purchased vaccines. We reviewed data to inform impact of the COVID-19 pandemic on HPV vaccination.

Methods: We present data on public purchased vaccine orders through the Vaccines for Children Program (VFC) for fiscal years (FY) 2019 through 2022 (as of February 13, 2022) and compare vaccine orders for FY2020-2022 (pandemic period) to FY2019 (pre-pandemic period). We also present 2019 and 2020 vaccination coverage data from the National Immunization Survey (NIS)-Teen.(1) NIS-Teen includes adolescents aged 13-17 years; the survey assesses vaccinations received throughout life, not limited to those administered in the survey year. Immunization data in NIS-Teen are from provider verified records.

Results: Public purchase HPV vaccine orders significantly decreased soon after the national emergency for COVID-19 was declared. During FY2020, HPV vaccine orders decreased 25% (1,026,593 doses) compared to FY2019. HPV vaccine orders improved in FY2021 but continued to be lower than in FY2019 (decrease of 9%; 391,101 doses). As of February 13, 2022, HPV vaccine orders were still lower than during the same time period in FY2019. HPV vaccination coverage (≥1 dose) among 13-17-year-olds in NIS-Teen 2019 and 2020, was 71.5% and 75.1%, respectively; up-to-date coverage was 54.2% and 58.6%. In 2020, most adolescents (73.6%) in NIS-Teen started the vaccine series before the pandemic began. Among those unvaccinated before March of the respective survey year, HPV vaccination initiation by April was lower in the 2020 survey than in the 2019 survey. The difference was largest in August/September (4.9 percentage points lower in 2020) but narrowed in subsequent months and was no longer significant by the end of November.

Conclusions: Public HPV vaccine orders through VFC in the United States significantly decreased in FY2020 and continue to be lower than pre-pandemic levels. Although national survey data show that coverage among 13-17-year-olds increased slightly in 2020 compared with 2019, most teens included in NIS-Teen 2020 started the HPV vaccination series before the pandemic began. While HPV vaccination coverage continues to improve, the HPV vaccination program is threatened by disruption of routine medical services due to the COVID-19 pandemic. Efforts are needed to increase coverage and to catch-up those who missed vaccinations over the past two years.

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SS06- Challenges in validation of new assays for cervical cancer screening and management of screen+ women

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#3971

NEW FINDINGS FROM THE VALHUDES STUDY: CLINICAL PERFORMANCE OF RIATOL QPCR HPV ASSAY ON SELF-COLLECTED VAGINAL AND URINE SAMPLES

13 - Self-sampling

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Background/Objectives: The VALHUDES framework was established to evaluate the relative clinical accuracy of HPV testing to detect cervical intraepithelial neoplasia grade 2 or higher (CIN2+) on self-samples versus matched clinician-taken cervical samples. In this study we evaluated the clinical performance of Riatol qPCR HPV assay.

Methods: 523 women referred to colposcopy due to previous HPV infection or cervical abnormality were recruited at five Belgian colposcopy centres (NCT03064087). First-void urine was collected at home with Colli-Pee device containing 7 ml conservation medium (Novosanis) the day before the colposcopy clinic. Vaginal self-samples were collected with Evalyn Brush (Rovers Medical Devices) [n=247] or Qvintip (Aprovix) [n=276] and matched cervical samples were taken by gynaecologists with a Cervex-Brush (Rovers Medical Devices). Both, vaginal and cervical samples were suspended in 20ml PreservCyt LBC vials (Hologic Inc.). Colposcopy and histological assessment of biopsies determined the outcome, defined as CIN2+. The Riatol qPCR HPV assay was used for HPV detection considering 0.0001 HPV copies/cell as positivity threshold.

Results: 494 sample triplets (median age: 40 years, range 19-71) with valid HPV test and biopsy/colposcopy results were included in the study. Riatol qPCR HPV assay on urine was as sensitive and specific as on cervical samples (relative sensitivity=1.00 [95%CI 0.97-1.03]; relative specificity=0.98[95%CI 0.89-1.08]). Likewise, the relative accuracy on vaginal samples taken with Evalyn vs on cervical samples did not differ from unity (relative sensitivity=1.00 [95%CI 0.97-1.03]; relative specificity=1.06 [95%CI 0.93-1.20]. However, the accuracy on vaginal samples taken with Qvintip versus on cervical samples were lower, although not significantly (relative sensitivity=0.91 [9%%CI 0.82-1.01]; relative specificity 0.89 [95%CI 0.80-1.00]). Sensitivity on vaginal samples collected with Evalyn Brush was higher than on samples collected with Qvintip (ratio=0.90 [95%CI 0.78-1.04]). We observed a significant decrease in ß-globin DNA concentration by age in vaginal samples, and a significant increase in cervical samples, no relation in urine.

Conclusions: Clinical sensitivity and specificity of the Riatol qPCR HPV assay on self-collected vaginal and first-void urine samples were not significantly different from clinician-taken cervical samples. However, accuracy tended to be lower in vaginal specimens taken with Qvintip.

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#3993

Validation of new rapid robust affordable HPV test based on CRISPR technology

09 - HPV testing

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Background/Objectives: Approximately 90% of cervical cancer cases and deaths occur in low- and middle-income countries (LMICs). Human papillomavirus (HPV) nucleic acid testing for cervical cancer screening which is well established in developed countries is more effective in preventing cervical cancer than cytology-based methods. The development of HPV tests that are affordable and do not require laboratory infrastructures is essential for LMICs.

Methods: The recent outbreak of SARS-CoV-2 paved the way for the development of new molecular tools for such methodologies for viral detection. The combination of an isothermal amplification with CRISPR-based technology for high-risk HPV detection may represent an interesting opportunity for a more efficient screening in LMICs.

Results: An overview of the emerging CRISPR-beased HPV testing will be provided. Several studies showed that the use of recombinase polymerase amplification (RPA) combined with CRISPR-Cas technology allowed specific and sensitive detection of individual or multiple high-risk HPV types in less than one hour of time. Our laboratory at the International Agency for Research on Cancer (WHO/IARC) is also evaluating this technology combined with E7 primers from a well validated multiplex HPV assay, the E7-MPG.

Conclusions: There is a still a need to clinically validate the use of this new technology for cervical screening and assess its applicability in low resource settings.

CS02- Cervical adenocarcinoma in situ: a review

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#3979

New Pathogenetic Classification for Invasive Adenocarcinoma of the Endocervix: Implications for the Clinician

26 - Cervical neoplasia

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Background/Objectives: In 2020, WHO updated the classification of endocervical adenocarcinoma. This new categorization was first championed by the International Endocervical Adenocarcinoma Criteria and Classification (IECC) in 2018.

Methods: Histologically, tumors are separated into the HPV-associated and HPV-independent categories based primarily on descriptive morphological criterion on routine H&E stains. The histologic subcategories of HPV-associated and HPV-independent cervical adenocarcinomas will be briefly discussed.

Results: Most cervical adenocarcinomas are HPV-associated and linked to HPV types 18, 16, and 45. Approximately 15% of cervical adenocarcinomas are HPV-independent. Clinically, stage is the most important prognostic variable; HPV-associated adenocarcinomas have a significantly better survival rate than HPV-independent adenocarcinomas of similar stage. Pattern of invasion is associated with risk for nodal metastasis.

Conclusions: This updated classification system and its clinical implications will be discussed.

References: WHO Classification of Tumours Editorial Board. Female genital tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.: vol. 4). https://publications.iarc.fr/592.

MSS02- HPV vaccines- special session

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#3801

VACCINATION OF OLDER ADOLESCENTS AND ADULTS WITH THE 9-VALENT (9vHPV) AND QUADRIVALENT (qHPV) HUMAN PAPILLOMAVIRUS VACCINES: EMERGING DATA FROM CLINICAL TRIALS AND REAL-WORLD STUDIES

06 - HPV prophylactic vaccines

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Background/Objectives: While HPV vaccination programs primarily target young adolescents prior to sexual debut, only a few countries have achieved high vaccine coverage rates in adolescents. As few countries have implemented catch-up vaccination programs in older adolescents and adults, many adults remain at risk for acquiring new HPV infections and HPV-related cancers and diseases throughout their lifespan. The qHPV and 9vHPV vaccine clinical trial programs included adult participants up to 45 years of age. Together with vaccine efficacy data from clinical trials, an understanding of the natural history of HPV infections in adult males and females, including patterns of HPV exposure through sexual activity and rates of HPV infection clearance, persistence, and progression to disease, is important to inform clinical decision-making regarding catch-up vaccination of adults.

Methods: N/A

Results: N/A

Conclusions: Presentations in this session will explore results from HPV vaccine efficacy and immunogenicity trials in males and females up to 45 years of age, including analyses in women after cervical surgery for HPV-related cervical disease. In addition, results from epidemiologic studies assessing patterns of sexual exposure to HPV in adults and the natural history of HPV infections in male and female clinical trial participants will be reported. Emerging post-marketing and cost-effectiveness analyses of HPV vaccination of high-risk adult populations will also be discussed.

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#3578

EFFICACY AND IMMUNOGENICITY OF THE QUADRIVALENT (qHPV) AND 9-VALENT (9vHPV) HPV VACCINES IN ADULTS: EVIDENCE FROM CLINICAL TRIALS

06 - HPV prophylactic vaccines

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Background/Objectives: The qHPV (HPV6/11/16/18) and 9vHPV (HPV6/11/16/18/31/33/45/52/58) vaccine clinical development programs included adult participants up to 45 years (y) of age.

Methods: Two randomized, placebo-controlled qHPV vaccine efficacy trials included women through age 45 y: the FUTURE III trial (NCT00090220; N=3819 aged 24-45 y), which was extended up to 10 y long-term follow-up (LTFU), and a 6.5 y trial in China (NCT00834106; N=3006 aged 20-45 y). 9vHPV vaccine efficacy was established in young women aged 16-26 y. QHPV vaccine efficacy in men aged 16-26 y was established in a placebo-controlled trial (NCT00090285; N=4065) which was extended up to 10 y LTFU, and immunogenicity was compared to that in men aged 27-45 y enrolled in a separate immunogenicity trial (NCT01432574; N=150). Two immunogenicity studies were conducted to demonstrate non-inferior immunogenicity in women aged 27-45 versus younger women (NCT03158220 [N=1212] and NCT03903562 [N=1300]). All vaccines were given as three doses (Day 1, Month 2 and 6); primary analyses were performed in per-protocol populations.

Results: In FUTURE III, qHPV vaccine efficacy was 88.7% (95% CI: 78.1-94.8) against HPV6/11/16/18-related persistent infection, cervical dysplasia and external genital lesions (EGL). Durable protection was observed through 10 y in LTFU, including a catch-up vaccination group (placebo recipients who received qHPV vaccine at age 32-50 y after the base study). Similarly, qHPV vaccine efficacy was 100% (95% CI: 32.3-100) against HPV16/18-related high-grade cervical dysplasia and 91.6% (95% CI: 66.0-99.0) against HPV6/11/16/18-related persistent infection in Chinese women aged 20-45 y. The qHPV vaccine prevented HPV6/11/16/18-related infection and disease (EGL, anal dysplasia) in men aged 16-26 y, with durable protection through 10 y in LTFU, including a catch-up vaccination group (placebo recipients who received qHPV vaccine at age 20-30 y after the base study). QHPV vaccine efficacy in men aged 27-45 y is inferred based on a cross-study analysis demonstrating non-inferior HPV6/11/16/18 antibody responses in men aged 27-45 y versus 16-26 y. In the 9vHPV vaccine trials, non-inferior geometric mean titers were observed in women aged 27-45 y versus younger women at Month 7 and >99% of women seroconverted to each vaccine HPV type. Based on these results, efficacy results previously demonstrated in women 16-26 y were bridged to women 27-45 y.

Conclusions: The qHPV and 9vHPV vaccines show efficacy and immunogenicity in adults through age 45 y. Adults not vaccinated as adolescents or young adults may benefit from qHPV or 9vHPV vaccination.

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#3691

Sexual behavior and patterns of partnerships in married and non-married adults in the United States: A Survey Study

06 - HPV prophylactic vaccines

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Background/Objectives: While the prevention of sexually transmitted infections such as Human Papilloma Virus (HPV) are often targeted in adolescents prior to sexual debut, adults may be at risk of acquiring HPV infections due to factors associated with their demographic and sexual attributes. Limited data on age-related sexual mixing and new sexual partnerships, a risk factor for HPV infections, are available. Such information can guide adult health care consumers and health care providers (HCPs) in decision making on HPV vaccinations. This study aimed to characterize new sexual partnerships among adults in the United States (US).

Methods: A cross-sectional online survey was conducted in 2019 among randomly selected healthy individuals from a general population online panel maintained by Kantar Health and its panel partners. Participants registered through a unique email address and completed an in-depth demographic registration profile. Inclusion criteria comprised of individuals aged 18-60, sexually active and provided consent. A quota sampling procedure mirroring the US Census 2017 data based on age groups and sex was applied to ensure a representative US sample. The survey collected data on socio-demographics and sexual behaviors. Sexual mixing matrices were generated for females, males, heterosexuals, women who have sex with women (WSW) and men who have sex with men (MSM). Data were analyzed to generate descriptive statistics stratified by marital status.

Results: A total of 2,036 respondents completed the survey, with 1,308 (64%) currently married/cohabitating and 728 (36%) not married/cohabitating. Mean (SD) age was similar between married/cohabitating individuals (39.3 (11.9)) and not married/cohabitating individuals (39.8 (13.7)). Females made up 51.1% and 51.2% of the married/cohabitation group and not married/cohabitating group, respectively. Married individuals reported a median (q1, q3) of 5 (2,10) lifetime sexual partners while not married individuals reported 6 (3, 14) lifetime sexual partners. Around 91.3% of married individuals and 59.9% of not married individuals reported at least one sexual partner in the past 12 months. At least one new sexual partner in the past 12 months was reported in 30.5% (399/1308) of married/cohabitating individuals and 35.2% (256/728) not married/cohabitating individuals; both groups reported a median (q1, q3) of 1 (1, 2) new partner(s). In terms of sexual mixing, a total of 427 heterosexual females, 782 heterosexual males, 215 WSW, and 212 MSM reported 815,1193,397 existing and 654 new partnerships. A higher proportion of partnerships with younger partners was found in male respondents, compared to female respondents.

Conclusions: Our study provides detailed insights into sexual behavior and sexual relationships among adult men and women in the US. New partnerships among mid-adults regardless of marital status, were observed in our study which may increase risk of exposure to new HPV infections. These data could provide needed evidence for healthcare consumers, HCP's and policy makers on decision making for adult HPV vaccinations in the US.

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#3399

TYPE-SPECIFIC CLEARANCE RATES OF PREVALENT AND INCIDENT HPV INFECTION IN YOUNG WOMEN

03 - Epidemiology and natural history

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Background/Objectives: Human papillomavirus (HPV) type-specific clearance rates of incident and prevalent infections were assessed in young women participating in a global HPV vaccine clinical trial (NCT00092482).

Methods: Anogenital swabs were collected at trial entry (day 1) and every 6 months over 48 months and analyzed for 9 high-risk HPV types (16, 18, 31, 33, 35, 45, 52, 58, and 59) in 1788 women aged 16-23 years from the placebo arm. Kaplan-Meier methods were used to estimate time to clearance of infections prevalent at Day 1 and incident infections that were identified during follow-up among women negative for all tested HPV types at trial entry (N = 1049). Type-specific HPV infection clearance was assumed to occur at first study visit in which a swab tested negative for a specific HPV type that had previously tested positive. Clearance was also defined as time to second negative swab at 2 consecutive study visits.

Results: The most frequent types detected on day 1 were HPV16 (129 of 1788 participants [7%]), HPV52 (78 of 1788 participants [4%]), and HPV31 (71 of 1788 participants [4%]). Approximately 68% (HPV52) to 85% (HPV59) of prevalent infections cleared (first negative swab) by month 18 and 87% (HPV52) to 95% (HPV33) had cleared by month 36, whereas clearance (second negative swab) was 43% (HPV52) to 63% (HPV33) by month 18 and 76% (HPV35) to 89% (HPV59) by month 36. The most frequent incident infections were HPV16 (202 of 1049 participants [19%]), HPV52 (113 of 1049 participants [11%]), and HPV59 (107 of 1049 participants [10%]). Approximately 56% (HPV52) to 87% (HPV35) of incident infections cleared (first negative) within 18 months and 83% (HPV58) to 100% (HPV33, HPV35, HPV52, and HPV59) cleared within 36 months, whereas clearance (second negative) was 28% (HPV35) to 47% (HPV59) within 18 months and 73% (HPV45) to 100% (HPV33/35) within 36 months. Differences between HPV types were not statistically significant.

Conclusions: Irrespective of HPV type, most prevalent and incident infections clear within 36 months in young women. Clearance rate estimates can vary considerably depending on HPV type and how clearance is defined.

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#3582

EFFECT OF THE 9-VALENT HUMAN PAPILLOMAVIRUS (9vHPV) VACCINE IN A SUBGROUP OF FEMALE CLINICAL TRIAL PARTICIPANTS WHO UNDERWENT CERVICAL SURGERY

06 - HPV prophylactic vaccines

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Background/Objectives: The 9vHPV vaccine prevents infection and disease related to HPV6/11/16/18 (quadrivalent HPV [qHPV] vaccine) and five additional high-risk HPV types (HPV31/33/45/52/58). We performed a post-hoc analysis on the development of 9vHPV vaccine type-related disease subsequent to cervical surgery in a subgroup of female participants.

Methods: Three international, randomized, double-blind studies were conducted in women aged 16-26 years (NCT00543543: 9vHPV vaccine [n=7106] vs qHPV vaccine [n=7109]; FUTURE I [NCT00092521] and FUTURE II [NCT00092534]: qHPV vaccine [n=8810] vs placebo [n=8812]). Participants included in the analysis underwent cervical surgery and had ≥6 months' follow-up post-surgery. Outcomes were incidence of HPV6/11/16/18-related condyloma, cervical (CIN), vulvar (VIN), and vaginal intraepithelial neoplasia (VaIN) in 9vHPV vaccine versus placebo recipients from the FUTURE I/II studies and incidence of HPV31/33/45/52/58-related disease in 9vHPV versus qHPV vaccine recipients from the 9vHPV vaccine study.

Results: There were 295 9vHPV vaccine recipients, 493 placebo recipients, and 313 qHPV vaccine recipients (from NCT00543543) who met analysis inclusion criteria. Prior 9vHPV vaccination was associated with reduced incidence of HPV6/11/16/18-related condyloma, CIN, VIN, and VaIN at ≥6 months post-surgery (95.4% [95% confidence interval [CI]: 74.7-99.8] vs placebo; incidence: 1.3 vs 29.0 per 1000 person-years) and reduced incidence of HPV31/33/45/52/58-related disease (86.3% [95% CI: 47.5-97.8] vs qHPV vaccine; incidence: 2.7 vs 19.4 per 1000 person-years). Incidence of high-grade CIN, VIN, and VaIN among 9vHPV vaccine recipients tended to be lower than in the relevant comparator groups (HPV6/11/16/18-related high-grade disease incidence: 1.3 [95% CI: 0.0-7.4] vs 4.4 [95% CI: 1.2-11.2] per 1000 person years in placebo recipients; HPV31/33/45/52/58-related high-grade disease incidence: 1.3 [95% CI: 0.0-7.4] vs 7.7 [95% CI: 2.8-16.7] per 1000 person-years in qHPV vaccine recipients).

Conclusions: Prior vaccination with 9vHPV vaccine was associated with reduced incidence of 9vHPV vaccine type-related disease in women undergoing cervical surgery.

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#3751

INCIDENCE OF PERSISTENT HPV INFECTION AND PROGRESSION OF INFECTION TO ASSOCIATED ANOGENITAL DISEASE AMONG MEN IN A GLOBAL HPV VACCINE TRIAL

03 - Epidemiology and natural history

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Background/Objectives: International data on anogenital HPV infection incidence and progression to associated disease among men are limited.

Methods: Data from 295 men who have sex with men (MSM) and 1576 heterosexual men (HM) aged 16-27 years in the placebo arm (unvaccinated men) of a 4-valent (4v) HPV vaccine trial (NCT00090285) were used to estimate: incidence rates of persistent anogenital HPV infections (penile/scrotum, perineal/perianal, anal) for 4vHPV (6/11/16/18) and 9-valent (9v) HPV (6/11/16/18/31/33/45/52/58) vaccine types; rates of progression of incident persistent infections to genital warts (GW), penile intraepithelial neoplasia (PeIN), and anal intraepithelial neoplasia (AIN); and HPV-type distribution in GW, PeIN, and AIN. Kaplan-Meier methods estimated cumulative incidence of persistent infections; and progression of infections to diseases (GW and PeIN in HM and MSM; anal condyloma and AIN in MSM only) based on swab specimen results, over 36 months.

Results: Among MSM, respective incidence (per 100 person-years) of persistent infection for 4vHPV and 9vHPV types was 7.0 (95%CI=4.9-9.7) and 9.1 (6.8-11.8) at penile/scrotal, 8.2 (5.4-11.8) and 9.8 (7.1-13.1) at perineal/perianal, and 14.1 (10.8-17.9) and 16.6 (13.4-20.2) at anal sites; incidence rates among HM were 4.2 (3.6-4.9) and 6.7 (5.9-7.6) at penile/scrotal, and 2.3 (1.8-3.0) and 3.1 (2.5-3.9) at perineal/perianal sites (Table). Cumulative incidence of progression from incident persistent infection (any 9vHPV type) was 1.1% for PeIN and 12.1% for GW among HM; and 8.0% for GW, 39.7% for anal condyloma/AIN1, and 35.0% for AIN2/3 among MSM (no incident infections progressed to PeIN among MSM). The most common HPV types in GW were HPV6 (HM=62.3%, MSM=50%) and 11 (HM=24.6%, MSM=41.7%). Among MSM, predominant HPV types in anal condyloma and AIN1 were HPV6 (60.6%/52.2%) and 11 (36.4%/17.9%); in AIN2 and AIN3 these were HPV6 (26.5%/29.6%), HPV16 (16.3%/29.6%), and HPV 11 (12.2%/18.5%). HPV types 18 and 31 were also frequently reported in AIN3 (18.5% and 25.9%, respectively).

Conclusions: A substantial proportion of unvaccinated HM and MSM developed incident persistent anogenital infections with ≥1 9vHPV types over 36 months. A high proportion of MSM with incident persistent anogenital infection also progressed to anal disease. Progression of incident persistent infection to PeIN was low among both HM and MSM, but a larger proportion progressed to GW.

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#3805

MODELING HEALTH IMPACT AND COST-EFFECTIVENESS OF HPV VACCINATION IN HIV+ AND HIV- MEN WHO HAVE SEX WITH MEN IN GERMANY

36 - Economics and modelling

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Background/Objectives: Men who have sex with men (MSM) have significantly increased incidence of human papillomavirus (HPV) infection as well as related diseases, mainly of the anus. Although HPV vaccination for boys aged 9-14 (catch-up 15-17) has been recommended in Germany since 2018, the MSM population above age 17 currently benefits little from the respective herd protection. A model that had been developed and used in previous work (EUROGIN 2021, Abstract #2200, IPVC 2021 Abstract #933) has now been updated to account for new data and assumptions for key drivers of the vaccine's value for a targeted nonavalent HPV vaccination program for MSM in Germany.

Methods: A model of HPV infection and disease among HIV+ and HIV- MSM was previously adapted to Germany and used to analyze the value of targeted nonavalent HPV vaccination. In this work we have updated the vaccination rate of adolescent boys (34% vs. 22.3% in our original analysis) that is projected throughout the time horizon of 100 years, we have assumed an increased uptake of vaccination among HIV+ MSM , and we have included genital warts in the analysis. We have estimated the public health and health economic outcomes over 100 years across various vaccination scenarios among MSM, including averted cases of and deaths from anal, penile, and oropharyngeal cancers, as well as averted cases of genital warts. Averted treatment costs and quality of life gained were also considered.

Results: In our previous work we had established the cost-effectiveness of HPV vaccination of MSM up to age 45 (ICER of 31,998 €/QALY) on the basis on averted anogenital and oropharyngeal cancers. In the present work, across the whole MSM population (both HIV+ and HIV-) and across the considered vaccination scenarios (varying age groups and uptakes), 1,923 to 4,218 cases of anogenital cancers are averted, along with 936 to 2,081 cases of oropharyngeal cancers, and 81,372-160,997 cases of genital warts. 1,143 to 2,605 cancer-related deaths are averted. For health economic results, we estimated ICERs between 24,314 to 39,057 €/QALY for the various MSM vaccination scenarios when compared to adolescent boys-only vaccination.

Conclusions: Vaccination of MSM with a nonavalent HPV vaccine will avert significant cases and deaths due to HPV-related cancers among MSM in Germany, will greatly impact the incidence of genital warts, and will have a meaningful health-economic impact.

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#3573

RISK FACTORS FOR HPV INFECTION AND DISEASE IN ADULTS: A LITERATURE SUMMARY

24 - Risk management

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Background/Objectives: A lack of consensus regarding which adults should be targeted for human papillomavirus (HPV) vaccination and vaccination cost reimbursement barriers have likely contributed to low HPV vaccination coverage rates. To help guide policy development, clinical decision-making, and further research, we summarized literature on risk factors for HPV infection and related disease.

Methods: MEDLINE, MEDLINE-IN-PROCESS and EMBASE databases were searched for observational studies published between 2009 and 2020 that reported relative risks or odds ratios for factors associated with HPV infection or disease. The results were qualitatively assessed using predetermined criteria.

Results: 153 studies met the selection criteria. HIV-positive (HIV+) status was strongly associated with HPV infection (some studies with >10-fold increased risk in cervical infection among HIV+ women, and penile and anal infections in HIV+ men who have sex with men [MSM]). Other factors with strong associations to HPV infection included number (>5) of sex partners (cervical, vaginal, and penile infections), a history of genital warts (GW) or sexually transmitted infections (vaginal, cervical, penile, anal, and oral infections), oral contraceptive use (cervical infection), inconsistent condom use (vaginal and penile infections), no prior pregnancy/childbirth (cervical infection), and a diagnosis of lupus (cervical infection). Inverse associations with age were often found in women but not in men. Women's marital status was inconsistently associated with HPV infection. Data regarding factors associated with oral infection were limited. Factors associated with HPV-related disease were less commonly reported but included a history of GW and smoking for cervical HPV-related disease, and a history of GW and receptive anal sex for anal HPV-related disease. Differences in study design and inconsistent reporting of risk factors limited comparisons across studies.

Conclusions: Our review confirmed the identification of some risk groups and risk factors widely believed to be strongly associated with adult HPV infection (e.g., HIV+, number of sex partners, MSM). An inconsistent association that was found between women's marital status and HPV infection may be notable, particularly if providers assume that married patients are not at risk. Other potential risk factors for HPV infection (including those for men throughout adulthood) and risk factors for HPV-related disease require more investigation and confirmation. Further research could help guide policymaking and clinical decision-making for adult HPV vaccination.

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#3012

REAL WORLD EVIDENCE OF 4VHPV/9VHPV VACCINE EFFECTIVENESS AND IMPACT IN HIGH-RISK POPULATIONS

06 - HPV prophylactic vaccines

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Background/Objectives: Our objective was to systematically identify and qualitatively synthesize real-world evidence (RWE) on vaccine effectiveness and population-level impact of 4vHPV and 9vHPV vaccines in specific high risk populations: women with pre-existing HPV-related anogenital diseases, men who have sex with men (MSM), immunocompromised or immunosuppressed individuals, including HIV(+), transgender and non-binary individuals, female sex workers, and people with recurrent respiratory papillomatosis (RRP).

Methods: A systematic literature review was performed using a pre-defined search strategy in Embase and MEDLINE. Articles published at any time and conference abstracts published in 2018 or later were searched on February 2, 2021. Records were reviewed and included studies were extracted by 2 independent reviewers. For each population, vaccine effectiveness and impact were extracted or calculated from available evidence for each HPV-related disease outcome of interest: anogenital precancers/cancers, head and neck precancers/cancers; genital warts; and RRP (vaccine effectiveness against recurrent disease only). HPV infection was not included as an outcome.

Results: From 2216 records identified, 30 were included: 25 vaccine effectiveness and 5 impact studies. The most vaccine effectiveness studies were found for RRP patients (N=12), followed by women with previous HPV-related anogenital disease (N=8), MSM (N=3), and immunocompromised or immunosuppressed individuals (N=2). All 5 impact studies were in HIV(-) MSM. No studies of transgender and non-binary individuals or female sex workers were found. Further, there were no studies of anal precancer/cancer in women nor any of vaginal, penile, or head and neck precancer/cancer in any group. Studies varied in their quality and findings. RWE supported vaccine effectiveness in reducing disease recurrence in RRP patients and subsequent disease among women with prior cervical disease. Vaccine effectiveness evidence strength was graded as high only for these groups. Vaccine effectiveness evidence strength was graded as medium for women with other anogenital diseases and HIV(-) MSM. For HIV(+) MSM and immunocompromised or immunosuppressed individuals patients, it was graded as low. Evidence strength for impact in HIV(-) MSM was also low.

Conclusions: RWE on the effectiveness and impact of 4vHPV and 9vHPV vaccines among high-risk populations is strongest for those receiving the vaccine for prevention of subsequent disease, specifically women with prior cervical disease and RRP patients. Significant data gaps remain regarding both populations at increased risk for HPV-related disease and specific disease outcomes. The evidence on vaccine effectiveness and impact among MSM, immunocompromised or immunosuppressed individuals, and HIV(+) populations is weak. No RWE is available for vaccine effectiveness and impact among transgender and non-binary individuals or female sex workers, highlighting the need for information on these vulnerable populations.

HN01- HPV and Head & Neck Forum - Screening, prevention and epidemiology

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#3571

EARLY DETECTION OF HPV-DRIVEN OROPHARYNGEAL CANCER IN PARTICIPANTS OF THE HAMBURG CITY HEALTH STUDY USING HPV16 E6 SEROLOGY

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: How oral HPV infections progress into oropharyngeal cancer (OPC) is poorly understood. The lack of detectable precancerous lesions makes early detection of HPV-driven OPC (HPV-OPC) difficult. Antibodies against HPV16 early proteins, especially E6, are strongly associated with incident but also prospective HPV-OPC. The majority (approximately 85%) of patients with incident HPV-OPC are seropositive for HPV16 E6 and at least one other early HPV16 protein.

Methods: We analyzed HPV16 antibodies in the first 5000 participants (n=4,424 sera) of the Hamburg City Health Study (HCHS), a population-based prospective cohort study (45 to 74 years) using multiplex serology. Individuals seropositive for HPV16 E6 and at least one additional early protein (E1, E2, E7) were considered at high risk for HPV-OPC and invited for six-monthly non-invasive head and neck examinations (visual inspection, endoscopy, ultrasound).

Results: Thirty-five participants (0.8%) were HPV16 E6 seropositive including eleven (0.3%) seropositive for at least one additional HPV16 early protein. One male (64 years) and one female (70 years) were identified with asymptomatic HPV16-driven tonsillar (pT2pN1) and base of tongue (BoT, pT1pN0) squamous cell carcinoma (SCC) within two years of clinical follow-up, respectively. Another male participant (62 years) had a chronic ulcer at the BoT during the first 6 months showing no signs of malignancy or dysplasia but chronic inflammation and HPV16 DNA and RNA positivity. After 12 months, he additionally presented with enlarged lymph nodes, and was diagnosed with an HPV16-driven BoT SCC (pT2pN1). Six individuals with high-risk HPV-OPC antibody profile were free of detectable symptoms and undergo regular follow-up. Two individuals were lost to follow-up.

Conclusions: Detection of HPV16 early antibodies might be an innovative method to identify asymptomatic HPV-OPC patients at an early stage, and may reduce morbidity and improve survival. The detected chronic ulcer prior to HPV-OPC diagnosis might represent a precancerous oropharyngeal HPV-driven lesion.

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#3952

Absolute risk of oropharyngeal cancer after an HPV16-E6 serology test and implications for screening

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The incidence of HPV-associated oropharyngeal cancer (OPC) is rising and earlier detection could be beneficial. The HPV16-E6 blood-based biomarker has high sensitivity and specificity for HPV-driven OPC, but the absolute risk of OPC following a positive or negative HPV16-E6 test is unknown.

Methods: We constructed an OPC risk prediction model that integrates data for (1) relative odds of OPC for HPV16-E6 serostatus, cigarette smoking, and sex from the HPV Cancer Cohort Consortium (HPVC3); (2) US population risk factor data from the National Health Interview Survey, and (3) US population OPC incidence and mortality.

Results: The 9 HPVC3 cohorts included 365 OPC cases with up to 10 years between blood draw and diagnosis and 5,794 controls. The estimated 10-year OPC risk for HPV16-E6 seropositive males at age 50 years was 16.7% (95%CI=10.5%-29.4%) and at age 60 was 25.0% (95%CI=15.5%-44.6%). Corresponding 5-year risk estimates were 7.0% and 13.3%, respectively. For HPV16-E6 seropositive females, 10-year risk estimates were 4.8% (95%CI=1.4%-11.4%) at age 50 and 7.5% (95%CI=2.3%-17.4%) at age 60, and 5-year risk estimates were 2.0% and 3.8%, respectively. Over 30 years, after a seropositive result at age 50, an estimated 48.1% of men and 16.6% of women would develop OPC. In contrast, 10-year risks among HPV16-E6 seronegative people were very low, ranging from 0.01% to 0.23% depending on age, sex, and smoking status.

Conclusions: We estimate that a substantial proportion of HPV16-E6 seropositive individuals will develop OPC, with 10-year risks of 17-25% for males and 5-8% for females aged 50-60 years in the US. The high risk of OPC among HPV16-E6 seropositive individuals may warrant periodic, minimally invasive surveillance, particularly for males, in regions where incidence rates reach levels that warrant such intervention. Establishing an appropriate protocol for this surveillance is an important direction for future research. This could involve evaluation of blood-based biomarkers and imaging techniques.

SS07B- Targeting high risk populations for control of HPV related cancer - Vaccination

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#3982

Assessing value of vaccine in women with cone

06 - HPV prophylactic vaccines

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Background/Objectives: HPV vaccination is the essential element in primary cervical cancer prevention. There is a growing body of evidence showing the value of HPV vaccination in the context of cervical excisional surgery.

Methods: We conducted a meta-analysis analysing the effect of pre- or post-conization vaccination (bi- or quadrivalent vaccine) against HPV. In the original meta-analysis from 2020 three retrospective and three prospective studies, three post-hoc analyses of RCTs and one cancer registry study were included after a systematic review of literature. Random-effect models were prepared to evaluate the influence of vaccination on recurrent CIN 2+.

Results: Ovarall, 21,059 patients (3,939 vaccinations vs. 17,150 controls) took part in the studies included in the meta-analysis. We observed a significant risk reduction for the development of new high-grade intraepithelial lesions after HPV vaccination (relative risk (RR) 0.41; 95% CI [0.27; 0.64]), independent from HPV type. There was a high heterogeneity between studies leading to a low level of evidence. The number of women needed to vaccinate before or after conization to prevent one case of recurrent CIN 2+ (NNV) is 45.5.

Conclusions: Our meta-analysis showed a significant risk reduction of developing recurrent cervical intraepithelial neoplasia after surgical excision and HPV vaccination compared to surgical excision only.

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#3985

HOW TO BECOME 'AT RISK' DUE TO AN ABANDONED VACCINATION POLICY: THE JAPANESE EXPERIENCE

06 - HPV prophylactic vaccines

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Background/Objectives: The Japanese Government provided emergency public funding for the HPV vaccine from November 2010 for girls 12-16yrs born after 1994. The HPV vaccine was formally included in the national immunization programme for girls 12-16yrs from April 2013. In June 2013, after unconfirmed reports of adverse events following immunisation appeared in the media, the Japanese government suspended proactive recommendations for the vaccine. Despite a large body of evidence supporting the safety of HPV vaccination, the suspension of proactive recommendation continued until April 2022, almost 9 years. During this time coverage declined rapidly from >70% to <1%, even though the vaccine was still included in the Japanese national immunisation programme and provided free of charge for girls in the target age group. This talk will focus on how an abandoned vaccination policy has increased Japanese women's risk of cervical disease.

Methods: Results of modeling and real-world data will be reported.

Results: Using the Policy-1 Cervix model, Simms et al (2020) estimated an additional 25,000 cervical cancer cases and >5,000 additional deaths among females born between 1994 to 2007 could occur over their lifetime compared to if coverage had remained at 70%. They also estimated that If coverage of < 1% continued, around 60,000 preventable cases and 10,000 preventable deaths due to cervical cancer could occur in Japan over the next 50 years, compared to if uptake had remained at 70%. However, they also found that if 70% coverage could be restored in 12 year olds in 2020 along with 50% catch-up coverage in girls 13-20 years using the 9 valent vaccine, 70%-80% of these cases and deaths could be prevented. Another study by Yagi et al (2020) estimated that the risk of cervical cancer was reduced by 41% in girls born in 1998 compared to those born in 1993. However, they found that the risk for girls born after 2000 was similar to those born in 1993. For real-world data, Sekine et al (2021) reported a 2.1% prevalence of HPV16/18 in women born in 2000 in Niigata prefecture compared to a 0.3% prevalence in women born between 1994 and 1999. Finally, Yagi et al (2022) reported a 5.04% prevalence of cytological abnormalities in Japanese women born in 2000, compared to a prevalence of 3.76% in women born between 1994 and 1999.

Conclusions: Both modeling and real-world data has shown that women born after 2000 are at increased risk of cervical cancer due to Japan's abandoned HPV vaccination policy, compared to those born between 1994 and 1999. The extent to which this damage can be mitigated depends on how quickly HPV vaccination coverage returns to former levels after reintroduction of proactive recommendations for the vaccine in April 2022 for girls 12-16yrs and those born between 1997 and 2005.

HN02 - HPV and HN Forum - Survivorship and surveillance

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#3995

Patient Preferences and Decision-Making among Patients with HPV-Associated Cancers

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The era of human papillomavirus (HPV) - associated oropharyngeal cancers has brought with it a treatment paradigm shift toward deintensification for patients at lower risk of recurrence with an eye toward preserving long-term quality of life. Patients with early stage oropharyngeal cancer (OPC) are a population with unique needs among head and neck cancer patients. Often, OPC patients have a choice of primary treatment between upfront surgery and upfront radiation therapy, regimens which quote equal survival, thus representing a situation of clinical equipoise and an opportunity for patient-centered counseling. This presentation will review the current understanding of patient preference in head and neck cancer treatment decision-making and will identify strategies for addressing the literature gaps and for conducting patient preference research within head and neck surgical oncology.

Methods:

Results:

Conclusions:

References:

MSS03- New evidence on the effectiveness of HPV vaccination against invasive cervical cancer: a global view

Lei Jiayao
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#3964

COUNTRY-SPECIFIC UPDATES ON HPV VACCINE EFFECTIVENESS AGAINST CERVICAL CANCER: SWEDEN

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 aimed to re-examine the effectiveness of qHPV vaccination against ICC with a longer follow-up period.

Methods: We conducted an updated analysis using the same methods as in our previous paper. We investigated the effectiveness of HPV vaccination against ICC in a national cohort study of 1,775,503 women aged 10-31 during 2006-2018 (we aim to further extend the follow-up to 2020 for the actual presentation, data application pending) utilizing Swedish registries. Girls and women that had at least one dose of qHPV vaccination were considered as vaccinated, and HPV vaccination was considered as a time-varying exposure. We assessed the association between HPV vaccination and the risk of 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) of ICC, 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.During the study period 28 HPV vaccinated women acquired ICC before age 32, while the corresponding number for unvaccinated women was 701, yielding an incidence rate of 0.90 and 6.19 per 100 000 person-year, respectively. The IRR for HPV vaccinated vs. unvaccinated women was 0.53, (95% CI 0.36 - 0.77) after adjustment of age and 0.38, (95% CI 0.26 - 0.57) after adjusting for other covariates. The IRR for women vaccinated before age 17 and age 17-30 were 0.23, (95% CI 0.10 - 0.53) and 0.45, (95% CI 0.29 - 0.70), respectively, after adjusting for all covariates.

Conclusions: In this updated analysis with extended follow-up period, qHPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level.

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#3969

REAL-WORLD HPV VACCINE EFFECTIVENESS STUDIES: GUIDEPOSTS FOR INTERPRETATION

06 - HPV prophylactic vaccines

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Background/Objectives: Registry-based effectiveness studies provide evidence for the real-world impact of the HPV vaccine. Given the length of time between acquisition of a "causal" HPV infection and cervical cancer, initial studies focused on the reduction of surrogate endpoints such as genital warts and cervical precancer.1,2 Now, studies from Denmark3 and Sweden4 document the impact of HPV vaccination on cervical cancer. However, the impact of vaccinating women past sexual debut into the late teens and 20s remains uncertain.

Methods: To guard against premature conclusions regarding the impact of HPV vaccination at older ages, we propose guideposts for analysis and interpretation of results from early studies.

Results: First, observational studies need to incorporate adequate follow-up time such that causal HPV infections acquired prior to vaccination can be observed through progression to cervical cancer, as well as adequate follow-up time postvaccination such that prevention of HPV infections could manifest as reductions in cervical cancer incidence (relative to unvaccinated individuals). Insight on the median age at causal infection can be inferred from microsimulation models.5 Second, potential biases inherent in observational studies (e.g., selection bias, comparability of follow-up time across groups, etc.) need to be accounted for. Third, the reduction in intermediate and cancer outcomes due to herd immunity may appear to attenuate vaccine effectiveness; analysis of time trends in outcomes among both vaccinated and unvaccinated women will be important to quantify the contribution of herd immunity to estimates of vaccine effectiveness. Finally, HPV vaccine effectiveness by age at vaccination may differ across settings with different HPV prevalence patterns;6 there is an urgent need for HPV natural history data and vaccine efficacy and effectiveness data from low-resource settings, particularly in sub-Saharan Africa.

Conclusions: HPV vaccine effectiveness studies show that HPV vaccination is effective at reducing early onset cervical cancer among girls vaccinated during adolescence. Determining a reasonable upper age limit for effective HPV vaccination will require extended follow-up for women vaccinated after adolescence; evaluation of time trends in HPV-related outcomes for evidence of herd immunity; and additional data on HPV natural history and vaccine effectiveness from settings with the greatest risk of cervical cancer.

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F13 - Microbiome

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#3703

METAGENOMES IN HPV NEGATIVE CERVICAL CANCERS

19 - Microbiome

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Background/Objectives: Background: Human papillomavirus (HPV) is a necessary cause of cervical cancer, although some invasive cervical cancers may test negative by HPV PCR. HPV-test negative cervical cancers may constitute a biologically distinct subgroup, associated with symptomatic detection, late-stage diagnosis and worse prognosis that may need different targeted therapeutic strategies. It is thus essential to find other biomarkers to early identify these HPV PCR negative cancers. Objective: We aimed to analyze and compare the metagenomes present in HPV PCR positive cervical cancers with the metagenomes present in HPV negative cancers.

Methods: Methods: We previously requested all invasive cervical cancers in Sweden during 10-year period and subjected them to HPV genotyping using Luminex. FFPE (formalin fixed paraffin embedded) specimens that were HPV PCR negative (392/29850), together with a set of 59 HPV PCR positive specimens (used as positive controls), were further subjected to an unbiased total DNA and cDNA sequencing using Novaseq 6000 in order to detect "truly" HPV negative specimens. A total of 223/392 cervical cancer cases were still negative for HPV after sequencing. For this study, we randomly selected 49/223 HPV negative specimens and compared the metagenomes present with the metagenomes detected in the 49 HPV PCR positive controls using the Kraken2. A total of 6 blank paraffin blocks were used as negative controls.

Results: Results: Overall, 53 bacterial genera were detected with the genera Klebsiella, Staphylococcus and Pasteurella often contributing to more than 75% of the total bacterial reads for each sample. No significant bacterial difference was found among HPV positive and HPV negative specimens. Analysis of viruses revealed a total of 50 viral genera showing more than 1% of the viral reads. Gorganvirus (known to infect vagina), Orthobunyavirus and Alphapapillomavirus represented most of the viral reads. HPV was only detected in the HPV PCR positive samples and no other significant difference was detected among the HPV PCR positive and HPV negative specimens.

Conclusions: Conclusions: Metagenomic analysis of bacteria and viruses present in HPV positive and HPV negative cervical cancers shows no significant difference in bacteria or viruses present, besides the HPV for HPV positive specimens.

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#3697

THE INTERPLAY BETWEEN HPV, CVM DYSBIOSIS AND CERVICAL CANCER DEVELOPMENT (MICROCERVIXHPV STUDY)

19 - Microbiome

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Background/Objectives: The importance of Cervico Vaginal Microbiota (CVM) in the protection against infections (as Human Papilloma Virus (HPV)) is already well established, namely through Lactobacillus species. Furthermore, is it also well-known the influence of HPV in the development of Cervical Neoplasia (CN). However, it is not possible to classify HPV as a complete carcinogen. That is why CVM dysbiosis should be explored, intending to decipher this curious interplay with HPV. This work aims to compare CVM composition of healthy women without HPV, HPV infected women and women in several Cervical Intraephithelial Neoplasia (CIN) and CN stages. Furthermore, it is intended to evaluate mortality and morbidity outcomes amongst all the groups as well as characterize the vaginal cytokine microenvironment, regarding each group and each CVM composition.

Methods: This is a national, longitudinal, observational and retrospective study that has 4 experimental groups (3-6) and 2 control groups (1,2), with 25 participants in each group, with the following composition: 1) HPV negative and without cervical lesions; 2) HPV positive and without cervical lesions; 3) HPV positive and CIN1; 4) HPV positive and CIN2-3; 5) HPV positive and CN without metastasis (T1-4 N0-2 M0); 6) HPV positive and CN with metastasis (T>2 N+ M+). DNA was isolated from cervicovaginal exudate samples, and then CVM, through bacterial 16s RNA was analysed by NGS. CVM cytokines were obtained through the analysis of cervicovaginal exudate in a Multiplex platform. Statistical analysis was performed in SPSS v 24.0. An alpha of 0.05 was considered statistically significant, and 95% confidence intervals were reported when appropriate.

Results: In terms of cytokine analysis, we expect a rise of inflammatory cytokines in patients with HPV infection, and the maintenance of this inflammatory process, could lead to CIN1-3 and, subsequently, CN. Furthermore, the levels of cancer-related cytokines might be dysregulated in patients with CIN1-3 and CN. Additionally, INF-gamma will probably be increased in all patients with active HPV infection. These cytokine profiles are in line with the changes observed in patients' CVM.

Conclusions: The importance of using cytokine profile and CVM is highlighted in the possibility of early detection/prevention of HPV and/or CIN/CN development. Furthermore, it can also be used as prognosis and treatment efficacy biomarker. Altogether, these insights are one step closer to personalized medicine.

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LONGITUDINAL STUDY OF VAGINAL MICROBIOME PRE AND POST TREATMENT IDENTIFIES BIOMARKERS FOR CERVICAL INTRAEPITHELIAL NEOPLASIA 3 (CIN3).

19 - Microbiome

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Background/Objectives: Increasing evidence suggests vaginal dysbiosis is associated with persistence of human papillomavirus (HPV) infection and cervical intraepithelial neoplasia (CIN 1-3) development. In this pilot longitudinal study we aimed to investigate the potential of vaginal microbiome biomarkers to predict CIN3 development in high risk HPV (hr-HPV) positive women.

Methods: A total of 59 women with normal cytology at initial screening and follow up time over six years were enrolled from the ARTISTIC randomised trial. The cohort included 14 HPV negative and 15 hr-HPV positive women through whole follow up time. Additionally 30 hr-HPV positive women, who developed CIN3 at the first follow-up, then surgically treated for the disease were testing HPV-negative were also included. Exfoliated cervical specimens were used as starting material for whole genomic and bacterial DNA extraction. Vaginal microbiota composition was determined by 16S rRNA gene fragments sequencing on Ion Chef Instrument. The S5 methylation classifier assays were performed as previously described (Brentnall et al, 2015).

Results: We identified unique microbial biomarkers associated with CIN3 development and recovery after surgical treatment. Hr-HPV positive women with CIN3 showed a significant overrepresentation of following microbial species: Sneathia amnii, Megasphaera genomosp., Peptosterptoccocus anaerobius and Achromobacter spanius. However, Sneathia amnii was the only bacteria consistently associated with CIN3 in all group comparisons performed ($p<0.01$). Conversely, after successful treatment women were hr-HPV negative and exhibited an increased representation of Lactobacillus species, especially Lactobacillus gasseri ($p<0.01$). Higher proportions of Lactobacillus helveticus, Lactobacillus suntoryeus and Lactobacillus vaginalis showed a potential protective role against CIN3 development in women with persistent hr-HPV infection.

Conclusions: We confirmed in our study S5 classifier scores are increasing with cervical disease severity. Increasing Sneathia amnii abundance was directly proportional to the S5 score increase during cervical disease development. This result might indicate its possible role in modifying the epigenetic landscape of the cervicovaginal space. Further investigations are required to establish a link between the identified potential vaginal microbiome biomarkers and their influence on epigenetic mechanisms.

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#3728

EFECTIVENESS OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HPV+ and HIV+ PATIENTS: A PILOT OBSERVATIONAL STUDY

34 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Immunosuppressed human immunodeficiency virus (HIV) -positive patients are at greater risk of incident, persistent, or recurrent human papillomavirus (HPV) infection. They also have lower clearance rate, higher viral load, and a marked predisposition for being colonized by several serotypes; all leading to more frequent and severe HPV-dependent lesions 1. A Colorius versicolor-based vaginal gel have shown to repair HPV-dependent low-grade cervical lesions and to increase high-risk HPV clearance in immunocompetent HPV-positive patients 2. The aim is to provide evidence about the effectiveness of a multi-ingredient Coriolus versicolor-based vaginal gel on HPV-dependent cervical alterations and HPV clearance in HIV+ patients

Methods: Pilot, prospective, one-cohort, observational study. 15 HIV-positive patients colonized by HPV in the endocervix region with an anomalous cervicovaginal cytology were included to receive a Coriolus versicolor-based vaginal gel 1 cannula/day for 21 days during first month + 1 cannula/alternate days for 5 months. Analysis of HPV patients with normal cytology and colposcopy image (improved alterations) and patients with HPV cleared (measured using hybrid capture test) is presented. The study was approved by an IRB and informed consent was signed by patients.

Results: The overall HPV clearance and cytological normalization rates were 73.33% and 80%, respectively. Endocervical colonization by HPV also partially cleared in 13.33% of the cases. At the end of the study, the normalization of the colposcopy anomalies associated to HPV was achieved in 55.56%.

Conclusions: Our results suggest that the proposed Coriolus versicolor-based vaginal gel treatment scheme could be an effective therapy in the management of endocervical HPV infection in HIV + patients. Its effects are similar to those obtained in patients without immunosuppression.

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MSS04- Routine HPV screening: how to modulate and manage HPV screening by age

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#3650

HPV-BASED CERVIX SCREENING AMONG WOMEN LESS THAN 30 YEARS OF AGE IN THE HPV FOR CERVICAL CANCER (FOCAL) TRIAL

10 - HPV screening

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Background/Objectives: Early studies on HPV-based cervix screening in women less than age 30 suggested a significant increase in colposcopy referrals that could overwhelm healthcare systems and unnecessary treatment for lesions that would otherwise regress. Thus, most guidelines delay HPV screening until age 30. However, recent evidence indicates that an increase in referrals may only occur in initial rounds of HPV screening. We used data from the HPV For Cervical Cancer (FOCAL) randomized controlled trial to investigate outcomes among participants aged 25-29 at baseline after two rounds of HPV screening.

Methods: Participants were randomized to two arms: HPV screening or cytology. Each arm received their respective test at Round 1 (HPV arm: 25-29 N=829, 30+ N=8723, Cytology arm: 25-29 N=834, 30+ N=8623) and co-testing (HPV/cytology) at 48-month Round 2 (HPV arm: 25-29 N=618, 30+ N=7726, Cytology arm: 25-29 N=611, 30+ N=7467). In this analysis, we only considered the result of each arm's respective primary exit test for colposcopy referral. Attendees were stratified by age group (inf30 or sup30) and we calculated percent referred to colposcopy at each round and with cervical intraepithelial neoplasia findings grade 2 (CIN2) throughout the trial and over 8 years of follow-up after trial exit.

Results: Across rounds, attendees in the younger age group had higher rates of colposcopy referral than the older age group in the same arm (Round 1: HPV - 25-29: 18.0%, 95%CI: 15.5, 20.7, 30+: 4.5%, 95%CI: 4.0, 4.9; Cytology - 25-29: 8.0%, 95%CI: 6.4, 10.1, 30+: 2.5%, 95%CI: 2.2, 2.8). In Round 1, referrals in the HPV arm were higher than in the Cytology arm for both age groups, however at Round 2 referrals were similar for corresponding age groups across arms (Round 2: HPV - 25-29: 5.3% 95%CI: 3.8, 7.4, 30+: 1.4%, 95%CI: 1.2, 1.7; Cytology - 25-29: 6.6%, 95%CI: 4.8, 8.8, 30+: 1.7%, 95%CI: 1.4, 2.0) and lower than Round 1. Among those inf30, throughout the trial, more CIN2 was detected in the HPV arm (N=30, 3.6%, 95%CI: 2.5, 5.1) than in the Cytology arm (N=16, 1.9%, 95%CI: 1.1, 3.1). After 8 years of follow-up the cumulative incidence of CIN2 was similar across arms (HPV: 5.1%, 95%CI: 2.3, 5.7; Cytology: 4.0%, 95%CI: 3.5, 6.7).

Conclusions: While colposcopy rates were higher in HPV-arm attendees aged 25-29 at Round 1, by Round 2 rates were similar between HPV and Cytology arms. More CIN2 lesions were detected among those inf30 in the HPV arm, resulting in more treatment of potentially regressive lesions. However, this difference decreased throughout long-term follow-up, suggesting that these precancers were detected earlier by HPV screening compared to cytology.

HN04- HPV and H&N Forum - submitted papers

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#3756

PREVALENCE AND INCIDENCE OF ORAL-HPV AMONG PEOPLE LIVING WITH HIV: WHAT DO WE KNOW?

03 - Epidemiology and natural history

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Background/Objectives: An upward trend of oropharyngeal cancer incidence is consistently being reported among men in middle and high resource countries, with a disproportionately higher incidence among people living with HIV (PLWH). Understanding the natural history of oral HPV among PLWH is needed to inform development of preventative and prognostic interventions to reduce the disproportionate burden of oral HPV infection and related disease. In general, there is a paucity of data on oral HPV natural history, particularly prevalence, incidence, and persistence. The aim of this study was to coalesce the existing knowledge regarding oral HPV among PLWH, individuals at highest risk of HPV-related oral cancers.

Methods: A systematic search of Medline and PubMed identified publications on prevalence and incidence of oral HPV infections among PLWH. For comparability, oral HPV findings were extracted from articles with all or at least 50% HIV-infected participants, similar sample collection method of oral rinse/gargle, and reporting of either any or high-risk (HR) oral HPV genotypes.

Results: Available data from 22 publications suggest oral HPV prevalence in PLWH from the USA ranged from 10-35% for any HPV and 13-15% for high-risk HPV (HR-HPV). Where HIV stratification was done, oral-HPV prevalence was 2-3 times higher among those with HIV compared to their HIV-uninfected counterparts. Publications from Europe (Netherlands, Italy, Portugal and Spain) reported oral HPV prevalence of 16-39% for any genotype and 12-25% for HR-HPV, with 1.3-3.0 times lower prevalence in HIV-uninfected individuals. Reports from countries such as Brazil, Thailand, and Mexico collectively reported 14-15% oral HPV prevalence of any genotype and 6-9% for HR-HPV. Only 5 manuscripts reported oral HPV incidence, 3 from the USA and 2 from the Netherlands and Italy, with combined incidence of 21-33/1000 person years for any HPV genotype and 10/1000 person years for HR-HPV in PLWH. Four out of five studies reported incidence in HIV-uninfected individuals at 10-15/1000 person years for any HPV and 0.2-6.5/1000 person years for HR-HPV.

Conclusions: There are scant data on oral HPV prevalence and incidence among PLWH globally. Available data suggest higher oral HPV prevalence in this population compared to the HIV-uninfected population. Similarly, incidence rates for any HPV are twice as high as in the HIV-uninfected. To investigate the disproportionate increase in oropharyngeal cancer among PLWH, the focus for future studies should be to elucidate the natural history of oral HPV and associated factors to inform development of preventative interventions.

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#3996

Detection of Circulating Tumor Human Papillomavirus DNA Before Diagnosis of HPV-Positive Head and Neck Cancer

15 - Molecular markers

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Background/Objectives: Human papillomavirus (HPV), most commonly HPV16, causes a growing subset of head and neck cancers (HNCs), including the majority of oropharynx cancers in many developed countries. Circulating biomarkers for HPV-positive HNC may allow for earlier diagnosis, with potential to decrease morbidity and mortality. The objective of this study was to determine whether circulating tumor HPV DNA is detectable in a greater proportion of archived plasma samples from individuals later diagnosed with HPV-positive HNCs than from cancer-free controls.

Methods: Cases were participants in a hospital-based research biobank with archived plasma collected at least 6 months before HNC diagnosis, and available archival tumor tissue for HPV testing. Controls were biobank participants without cancer or HPV-related diagnoses, matched 10:1 to cases by sex, race, age and year of plasma collection. Plasma and tumor tissue were evaluated for HPV DNA using a previously validated digital droplet PCR-based assay that quantifies tumor-tissue-modified viral (TTMV) HPV DNA.

Results: Twelve HNC patients with median age of 68.5 years (range, 51-87 years) were included. Ten (83.3%) had HPV16 DNA-positive tumors. ctHPV16DNA was detected in pre-diagnostic plasma from 3 of 10 (30%) patients with HPV16-positive tumors, including 3 of 7 (43%) patients with HPV16-positive oropharynx tumors. The timing of the plasma collection was 19, 34 and 43 months before cancer diagnosis. None of the 100 matched controls had detectable ctHPV16DNA.

Conclusions: This is the first report that ctHPV16 DNA is detectable up to several years before diagnosis of HPV16-positive HNC for a subset of patients. Further investigation of ctHPV16DNA as a biomarker for early diagnosis of HPV16-positive HNC is warranted.

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#3609

Experimental studies with combinations of targeted therapy on HPV positive and negative tonsillar and base of tongue cancer lines reveals synergistic effects

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human papillomavirus positive (HPV+) tonsillar and base of tongue squamous cell carcinoma (TSCC/BOTSCC) have a favorable outcome when compared to corresponding HPV-negative (HPV-) cancer, but upon relapse therapeutic options are limited. PIK3CA and FGFR3 are often mutated in HPV+ cancer and we have previously tested TSCC/BOTSCC cell lines (HPV+ CU-OP-2, -3 and -20 and HPV- CU-OP-17) with and without such mutations for their sensitivity towards PI3K and FGFR inhibitors alone and in combination and found variable effects, as well as synergistic effects upon their combination irrespective of whether the cell lines had corresponding mutations or not. In this report, we have extended our previous studies with these cell lines and have explored the effects of CDK4/6, PARP inhibitors either alone or together with PI3K and FGFR inhibitors and others.

Methods: HPV+ CU-OP-2 (with a PIK3CA and FGFR mutation), -3 and -20 (with a PI3K mutation) and HPV- CU-OP-17 were treated with PI3K inhibitor (BYL719), with FGFR inhibitor (JNJ-42756493), CDK4/6 inhibitor (PD-0332991) and PARP inhibitor (BMN-673) and others alone or in different combinations. Viability was analyzed by a WST-1 assay, while proliferation and cytotoxicity were tested by the IncuCyteTM S3 Live® Cell Analysis System.

Results: All CU-OP cell lines exhibited some sensitivity to single treatment of BYL719 (PI3K), JNJ-42756493 (FGFR) and PD-0332991 (CDK4/6) inhibitors and showed some enhanced effect after combination treatment of the individual inhibitors. However, sensitivity was/was not correlated to presence of FGFR/PI3K mutations. The cell lines are now being tested for their sensitivity to additional inhibitors such as WEE1 and p53 (APR-246). Additionally, the effect of the inhibitors on a molecular level will be tested via Western blotting.

Conclusions: All tested inhibitors exhibited an inhibitory effect on the viability of both HPV+ and HPV- CU-OP cells, irrespective if the presented FGFR/PI3K mutation status or not, and no enhanced sensitivity on the presence of FGFR or PI3K mutations was detected in the cell lines. However, when combining the PI3K and CDK4/6 inhibitors synergistic effects were disclosed in all cell lines suggesting that combining these different inhibitors could be a beneficial therapeutic opportunity and warrants further investigations.

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#3605

PROMISING EPIGENETIC BIOMARKER FOR IMPROVED DETECTION OF HEAD AND NECK CANCER IN NON-INVASIVE SPECIMEN

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Head and neck squamous cell carcinomas (HNSCC) are mainly diagnosed at advanced tumour stage after the onset of symptoms. Timely detection would significantly improve the options for successful treatment and thus contribute to a decrease in the mortality observed for this group of carcinomas. Consequently, non-invasive diagnostic tools for early and precise detection need to be established. We developed a qPCR-based assay for five human DNA methylation markers previously validated with tumour and control tissue. The assay aims at detecting the markers besides in tissue also in non-invasive specimen, such as mouth swabs and saliva. The OncSaliva study (principal investigator Prof Orlando Guntinas-Lichius) was designed as a feasibility study to determine the clinical performance of the DNA methylation marker assay.

Methods: Different commercial sample collection tools and an own saliva collection tool with corresponding sample stabilisation buffer were compared to evaluate the best method to determine DNA methylation markers in non-invasive specimen from the head and neck region. The OncSaliva trial is an ongoing trial where 100 tumour patients and a group of 100 controls will be included. At initial visit (time of surgery) tissue from the tumour and non-invasive specimens are collected. During follow-up visits, saliva and swabs will be taken. So far, all specimens were collected at the Department of Otorhinolaryngology, Jena University Hospital. Genomic DNA was isolated from tissue or saliva/swab samples with stabilisation buffer and bisulfite-converted. Detection of the DNA methylation markers (and bisulfite-specific reference Beta-actin, ACTB) is performed using realtime methylation-specific PCR on the bisulfite-converted DNA. The sensitivity and specificity in respect to methylation level and performance of the different sampling methods were calculated to evaluate the pereformance of the assay.

Results: Of the tools for swab collection the FLOQSwab® (Copan) and my-budget Swabs (Bio-Budget Technologies GmbH) performed best when used together with oncgnostics' own stabilisation buffer. This stabilisation buffer is also used in saliva collection. The FLOQSwab tool will be further employed in the ongoing study. So far, 26 cancer patients and 8 control patients were enrolled in the trial. The detection rate in tumour tissue was between 42% and 96%, depending on the methylation marker. Specificity was 100% for all markers. In saliva, the detection rate ranged between 18% and 73% in tumour patient samples, and specificity ranged between 75% and 100%. Matching results between tissue and saliva for the single DNA methylation markers occurred for minimal 52% and maximal 78% of specimen pairs in the HNSCC group.

Conclusions: DNA methylation markers may be utilized as reliable HNSCC markers. Preliminary results from the OncSaliva study show that DNA methylation is reliably detectable in all kinds of tested specimen types, tissue, swab and saliva. The five validated DNA methylation marker regions may provide the basis for first tests within head and neck cancer diagnostics, especially for post-surgical follow-up, the main medical focus of the OncSaliva study.

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#3709

Whole exome sequencing of HPV positive tonsillar and base of tongue squamous cell carcinomas reveals a global mutational pattern along with relapse-specific somatic variants

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: HPV+ tonsillar and base of tongue cancer (TSCC and BOTSCC) have a better prognosis than corresponding HPV- cancer. For this reason it has been suggested that patients with HPV+ cancer do not need the intensive chemoradiotherapy given today. Moreover unfortunately this treatment does not improve survival for those with a worse prognosis, so other alternatives such as e.g. targeted therapy would be of benefit. Nevertheless before tapering or personalizing therapy it is important to distinguish patients with a very good prognosis from those with a worse prognosis. To do so finding additional markers would be of great benefit. We have previously identified some useful prognostic markers such as e.g. high numbers of CD8+ tumor infiltrating lymphocytes (TILs), and presence of HPV16 E2 and others, but additional markers would be of use. For this purpose we wanted to perform whole exome sequencing of primary tumors from patients that relapsed and control patients that did not relapse and compare their primary tumor sequences for possible differences and similaritites.

Methods: Twenty TSCC/BOTSCC patients with recurrence and 20 patients without recurrence were identified at Karolinska University hospital during the period 2000-2014 were identified with available formalin fixed paraffin embedded samples. Forty-primary tumors and adjacent normal tissue were separated by micro-dissection from 20 patients with recurrence and 20 patients without recurrence. In addition, local recurrences or distant metastasis from patients that relapsed were also microdissected. DNA was then extracted from the samples and whole exome sequenced at SciLifeLab in Stockholm. Bioinformatic analysis was performed by SciLife Stockholm, NBIS/UPPMAX Uppsala and by us.

Results: Successful sequencing was obtained from primary tumors of 18 patients without recurrence and 17 patients with recurrence and from these patients successful sequencing was also possible from 10 recurrences (5 local recurrences and 5 distant metastasis). Moreover successful sequencing as obtained from 25/35 normal tissues of the primary tumors. The patient samples were first analysed for high/mmodifier/moderate impact variants but later for only high impact variants occurring separately in at least 30% of each cohort (i.e. those with or without recurrences). Subsequently also commonly occurring variants/genes i.e. occurring in at least 30% of the whole cohort were investigated for. One variant with a high impact indel the CDC27 gene was observed only in 5/17 patients with relapse, but in none of the primaries of patients without recurrence. In the primaries of patients without relapses other profiles were disclosed e.g. a substitution in the KCNJ12 gene was significantly enriched. In addition, some variants e.g. deletions in BCLAF and OVCH2 were common to the whole cohort. Furthermore, keratin and mucin associated genes were commonly affected in the whole cohort.

Conclusions: In conclusion, we found a specific CDC27 variant unique for tumors of HPV+ TSCC/BOTSCC patients which relapsed. In addition, we some genes that were frequently affected in the primary tumors of the whole cohort independent of outcome such as e.g. deletions in BCLAF and OVCH2 were common as well modifications in keratin associated and mucin associated genes.

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#3540

ATTRIBUTABLE FRACTION OF HPV IN ADVANCED STAGE HEAD AND NECK CANCERS PER GEOGRAPHICAL REGION: RESULTS FROM A SYSTEMATIC LITERATURE REVIEW - THE "ALARM' STUDY

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human papilloma virus (HPV) has been implicated in the pathogenesis of some head and neck cancers (HNC), particularly of oropharyngeal cancer (OPC). We present data on the prevalence of HPV, i.e., HPV attributable fraction (HPV AF), in advanced stage [locally-regionally advanced (LA) and recurrent/metastatic (RM)] HNC per geographical region as captured through a systematic literature review of the last decade.

Methods: For interventional studies (IS; i.e., phase I-III trials), clinicaltrials.gov was initially searched, followed by a search for abstracts/articles with available results using the corresponding NCT numbers in Pubmed and Embase databases and ASCO/ESMO journals of congresses. For non-interventional studies (NIS), MEDLINE and Embase databases were directly searched. Electronic searches were restricted by timeframe [01Jan2010 - 31Dec2020]. Criteria for study selection included: availability of HPV AF data for patients with LA and/or RM HNC, enrolled from 01Jan2010 onwards, with OPC included among HNC types. Single-continent studies were grouped into geographic regions as defined by the International Agency for Research on Cancer. Pooled results for IS and NIS are presented.

Results: Eighty-one studies (62 IS; 19 NIS) met the inclusion criteria, 52 of which also included HPV AF data specifically for OPC patients. Data was available for studies conducted in Northern America, Europe, Eastern Asia and multiple-continents; among 1923, 2804, 121, and 4759 patients with advanced stage HNC, respectively, at least 809 (42.1%), 710 (25.3%), 19 (15.7%) and 874 (18.4%) were HPV+. HPV AF in the aforementioned regions based on the mean of the reported HPV prevalence across studies was 46.0%, 24.7%, 20.1%, and 19.8%. In Northern Europe, Western Europe, Southern Europe, and multiple European regions (including Central and Eastern, Southern, and Western Europe), of 377, 1381, 284, and 762 patients with advanced stage HNC, 238 (63.1%), 325 (23.5%), 75 (26.4%), and 72 (9.4%) were HPV+, respectively. The respective reported mean HPV AF was 31.9%, 24.3%, 23.2%, and 17.2%. Patterns of geographic distribution were consistent based on analyses for the subgroup of OPC patients.

Conclusions: Despite variations across the globe, the HPV burden in advanced stage HNC and OPC in the last decade has been substantial. Based on published data, the highest HPV AF was observed in Northern Europe and Northern America, with at least one in three advanced stage HNC cases being HPV+. These results suggest a considerable number of advanced stage HNC cases are potentially preventable.

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#3508

HPV RELATED OROPHARYNGEAL CANCER : A MONOINSTITUTIONAL EXPERIENCE OF UPFRONT MINI-INVASIVE TRANSORAL SURGERY (TOS) VERSUS CURATIVE CHEMORADIATION

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oropharyngeal cancers (OPCs) can be treated with both non-surgical and surgical approaches. Human Papillomavirus (HPV) related OPCs usually present as small tumours with well detectable metastatic cervical lymph nodes at diagnosis. These tumours are amenable to mini-invasive transoral surgery (TOS), robotic or laser-assisted and concomitant neck dissection (ND)1,2. Retrospective data suggest high oncologic efficacy of TOS followed by adjuvant therapy compared with Chemoradiation (CRT) with a lower toxicity 3-5. The present study compares survival and treatment-related side effects of two cohorts of patients (pts) with HPV related OPC treated with curative Intesity-Modulated Radiation Therapy IMRT+/-CT or TOS followed by postoperative treatment.

Methods: We retrospectively reviewed all patients affected by OPC and treated at the European Institute of Oncology, IRCCS, from 2015 to 2020. Inclusion criteria: 1) advanced stages of squamous cell carcinoma HPV+ (III and IV according to AJCC 7th Ed) 2) patients treated with intensity-modulated radiotherapy IMRT (+/-CT) or TOS followed by postoperative radiotherapy (PORT) with or without concurrent CT. According to the smoke habits (>10 packs/year), the treatment's indications given by the local tumour board were: TOS for HPV+/smokers and IMRT (+/-CT) for HPV+/non smokers. Oncological outcomes evaluated were: overall survival (OS), progression-free survival (PFS) and locoregional control (LCR). The toxicity was evaluated in terms of need of Enteral nutrition, tracheotomy, and oesophageal stricture occurred at any time during the follow-up period

Results: A total of 96 pts matched inclusion criteria. The median age was 61 years (range 55-67), and 72% were male. Sixty (62.5%) pts underwent IMRT (90% with concurrent CT) while 36 (37.5%) pts have been treated with TOS followed by PORT (56% with concurrent CT). The median follow-up time was 29.61 months (range 0.30-77.77 months). The surgical cohort and pts treated with IMRT+/-CT had similar characteristics except for a higher rate of advanced-stage disease (stage III 28% vs 0% respectively p=0.002) and concurrent chemoradiation (90% vs 56%, respectively, p=0.001). OS, PFS and LRC in IMRT and TOS groups were 98% and 97%, 86% and 83%, 91,7% and 95% respectively. Eight (12%) and 4 (4%) pts required enteral nutrition during the radiation course in the IMRT and TOS group, respectively. Twenty-one (30%) and two (7%) pts lost more than 10% (G3 toxicity) of their baseline value in the IMRT and TORS cohort, respectively. Tracheostomy, enteral nutrition and oesophageal stricture occurred during the follow-up period in 6%, 3%, 0% and 1%, 3% and 0% of pts treated with IMRT and TOS, respectively

Conclusions: In our study pts with HPV-related OPCs treated with modern techniques (IMRT and TOS) experienced similar survival outcomes and a similar long term toxicity profile. TOS upfront surgery has demonstrated lower early toxicity; conversely, it seems to be similar in terms of late toxicity despite the more advanced stage of patients in the CRT cohort.

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#3115

Assessing the burden of HPV-Related Head and Neck Cancers in mainland China: The Design of BROADEN-China study

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: In the past two decades, persistent human papillomavirus (HPV) infection has been attributed to an increasing proportion of head and neck cancers (HNCs) worldwide. In China, national epidemiological data on HNCs disease burden and HPV attribution is currently limited. Thus, a study named BROADEN-China (The absolute burden of HPV-related head and neck cancers -- in China) is being conducted in mainland China from 2020-2023, to estimate the fraction of HNCs attributable to HPV per anatomic site, in 3 time periods (2008-2009, 2013-2014 and 2018-2019). This abstract describes the design of the BROADEN-China study.

Methods: Fourteen hospitals with locally archived HNC tissues will be selected from 7 regions nationwide. A stratified multi-stage non-randomized cluster sampling method will be applied to select tissue samples.

Results: Approximately 2540 patients over 18 years old with pre-treatment formalin-fixed paraffin-embedded tissue samples from the defined study time frame will be included into the study, involving the anatomic sites of oropharynx (n=819), oral cavity (n=551), nasopharynx (n=270), hypopharynx (n=311), and larynx (n=589). Well known risk factors for HNCs (e.g. smoking status, alcohol consumption, betel nut chewing, and teeth loss) will be collected from medical records. A strict combination of HPV testing (HPV-DNA, HPV-mRNA and p16 immunohistochemistry) and pathological diagnosis will be conducted at the central laboratory to report the proportion of HNCs attribute to HPV in the study population per anatomic site and year.

Conclusions: The understanding of burden and temporal trend of HPV-related HNCs in China will help health care providers, policymakers, and other stakeholders to understand the value of HPV vaccination programs for both female and male. In addition, the approaches established in BROADEN-China will serve as a methodological framework for epidemiological research on HPV-related HNCs in mainland China in the future.

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#4000

The value of p16 and HPV DNA in non-tonsillar, non-base of tongue oropharyngeal cancer

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Background: Oropharyngeal squamous cell carcinoma (OPSCC) is dominated by tonsillar and tongue base carcinomas (TSCC/BOTSCC), but there are carcinomas at other sites, such as uvula/soft palate/ pharyngeal wall here defined as other OPSCC. Human papillomavirus (HPV) positive TSCC/BOTSCC have favorable outcome, and the TNM-classification separates OPSCC into HPV mediated (p16INK4a overexpressing, p16+) and HPV unrelated OPSCC (p16INK4a non-overexpressing, p16-) cancer, but the prognostic role of p16+ in other OPSCC is unclear. Aims/Objectives: This study therefore aimed to further investigate the prognostic role of p16 +, presence of HPV DNA, or both combined in other OPSCC.

Methods: Material and methods: 195 other OPSCC, from patients diagnosed 2000-2018 were tested for p16, and/or presence of HPV DNA and the data correlated to outcome.

Results: Results: Neither overall survival, nor disease free survival correlated to presence of p16+ or HPV DNA in other OPSCC. p16+ and HPV DNA presence were correlated (p<.0001), but the sensitivity of p16 as a surrogate marker for presence of HPV DNA was low (49%).

Conclusions: Conclusions and significance: The data suggest that p16+ (and p16+/HPV DNA) positive other OPSCC should be analyzed cautiously and possibly separately from the HPV mediated OPSCC staging group.

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CS03- New developments in colposcopy practice

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#3984

VALcolp: A protocol for clinical validation of portable colposcopy devices

25 - Colposcopy

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Background/Objectives: Technical advances in medical imaging and artificial intelligence-based interpretation of digitized images have generated new optical devices that allow assisted visual assessment of the cervical surface applicable in remote low-resource areas as well as adjunctive sophisticated tools (e.g., spectroscopy, other optical processes) that may improve the quality of current colposcopy practice in well-equipped gynaecologic centres in high-income countries. However, their clinical accuracy for cervical precancer is poorly documented in peer-reviewed scientific literature and there is an urgent need for robust clinical validation of these new devices. VALcolp is a framework for validation and comparison of colposcopy devices involving a group of centres-of-excellence with world-widely recognized expertise in the field of management of cervical precancer. VALcolp aims to evaluate the relative sensitivity and specificity of new visual devices (simplified or advanced) to detect cervical precancerous lesions compared to high-quality standard colposcopy using histological assessment of biopsies as reference.

Methods: The core VALCOLP protocol follows principles of diagnostic test accuracy where the index test (new colposcopy device) and the comparator test (standard colposcopy) are applied to 500 women enrolled at colposcopy clinics and who subsequently have biopsies taken. The histological assessment of biopsies will be used as reference standard. All tests are applied at the same colposcopy visit and, where applicable, the result of the firstly performed test will be blinded to the assessor prior to performing the second test. Local adaptation of the generic protocol according to context and capacity may be considered.

Results: VALcolp will generate robust test accuracy data for multiple new colposcopy devices. VALcolp completed with literature data will yield a rich database that may be used to define internationally agreed criteria for validation of new generation colposcopy devices.

Conclusions: ValCOLP is an ambitious concept that finally will inform stakeholders which colposcopy devices may be considered as clinically validated.

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SS11- Innovative SARS-CoV-2 diagnostic devices: opportunity for worldwide HPV screening

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#3976

Commercial HPV tests: what's on the market and what's not (and what we desperately need)?

01 - HPV disease and COVID-19

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Background/Objectives: Molecular tests for detection of human papillomaviruses (HPV) play a crucial role in the prevention of cervical cancer, including announced WHO's elimination efforts. HPV testing is a recommended approach for cervical cancer screening of women over 30 and for management of those with precancerous cervical lesions. In addition, they are widely used in epidemiological studies, HPV surveillance and vaccination impact monitoring. We present here the 2020 update of the inventory of commercial molecular HPV tests available on the market and outline implications for future research and policies.

Methods: Data from our internal files were retrieved and reviewed and a detailed search using Medline/Pubmed, Web of Science, Scopus, Google Scholar, Google and Bing, without language or period restrictions, was performed in September 2019 and again in January 2020.

Results: We have identified at least 254 distinct HPV tests (and 425 test variants) on the global market in 2020, which represent significant increase in comparison to 2015. Unfortunately, this increase came mostly in terms of quantity and at the detriment of quality. Current situation is quite alarming since 60% of the HPV tests on the global market are without a single peer-reviewed publication, 82% lack any published analytical and/or clinical evaluation, and over 90% are not evaluated in line with consensus requirements that ensure safe use in clinical settings.

Conclusions: Although COVID-19 pandemic had negative impact on cervical cancer control it might also generated opportunities for more efficient prevention. However, significant challenges in post COVID-19 era remains for both the HPV scientific community and the manufacturers of HPV tests.

SS12- The role of HPV circulating DNA for the surveillance of cancer recurrence in HPV-associated cancer

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#3967

HPV CTDNA AS A MARKER FOR EARLY DETECTION OF RELAPSE IN CERVICAL AND ANAL CANCERS

15 - Molecular markers

Background/Objectives: Almost all cervical cancers (CC) are caused by human papillomavirus (HPV) which may be also responsible for other anogenital cancers, such as anal squamous cell carcinoma (ASCC). Chemoradiotherapy is the current standard care for locally advanced cervical or anal 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.

Methods: We analyzed serum samples from patients with HPV16- or HPV18-related CC or ASCC. Samples were collected before and after treatment. 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 ($p=0.01$). In the cohort of patients with ASCC, HPV ctDNA was detected in 88% (29/33) of the patients, HPV ctDNA levels were also associated with tumor stage ($p=0.008$) and lymph node involvement ($p=0.03$). Complete clearance of HPV ctDNA by the end of treatment was significantly associated with a longer PFS ($p<0.0001$) in both cohorts. In the cervical cohort, 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.

Conclusions: Circulating HPV DNA may be a useful marker to identify patients at risk of relapse of CC or ASCC.

MSS06- Assessing risk of cervical cancer in the post-vaccination era

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#3962

Cellular methylation markers in the CIN triage of HPV-vaccinated women

18 - Methylation

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Background/Objectives: HPV vaccination programs will impact the choice of optimal screening strategies. Owing to the reduced incidence of cervical (pre)cancer in vaccinated women, the predictive value of a positive screening result may decrease and the proportion of false-positive results, and associated unnecessary referrals and costs, could increase, if screening programs are not adapted to vaccinated women. Host cell DNA methylation markers (e.g., FAM19A4, miR124-2) provide a molecular means to identify women with cervical cancer and advanced high-grade CIN. Host cell DNA methylation analysis has the ability to discriminate CIN2/3 lesions with a high short-term risk of progression to cancer by a tumor-like, or high-risk methylation pattern. This presentation will discuss the potential of host cell methylation markers in the context of HPV-vaccinated women.

Methods:

Results:

Conclusions:

References:

LW 03- Zervixkarzinomscreening in Deutschland und international - Teil A - Deutschland

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#3983

Kann das Einladungsmodell die Teilnehmerzahl erhöhen

11 - Screening for women difficult to reach

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Background/Objectives: 2020 wurde in Deutschland die neu organisierte Zervixkarzinomvorsorge mit Co-Testing (HPV-Test + Zytologie) in 3-Jahres-Intervallen für alle Frauen ab 35 Jahren gestartet. In der Vergangenheit lag die Teilnahmerate bei etwa 70 % in einem Zeitrahmen von drei Jahren. Die Nicht-Teilnehmerinnen haben ein höheres Risiko, an invasiven Gebärmutterhalskrebs zu entwickeln. Die Bereitschaft zur Teilnahme kann durch Einladungsschreiben oder das Angebot von Selbsttests für die häusliche Anwendung verbessert werden.

Methods: In der Hannoverschen Self-Collection Studie (HaSCo-Studie) evaluieren wir einen systematischen Ansatz zur Selbstuntersuchung auf humane Papillomaviren (HPV) bei Personen, die nicht am regulären Screeningprogramm teilnehmen. 20.000 Frauen im Alter von 30 bis 65 Jahren aus der Region Hannover, Niedersachsen, wurden nach dem Zufallsprinzip (Stichprobe des Melderegisters) rekrutiert. 10.000 Frauen erhielten direkt einen HPV-Selbsttest nach Hause geschickt, die anderen 10.000 ein Informationsschreiben mit der Möglichkeit zur Teilnahme an der Studie (Opt-out- bzw. Opt-in-Strategie). Es wurde eine Schichtung nach Alter (7 Kohorten) und Wohnort (Stadt vs. Land) vorgenommen.

Results: Zum Eurogin Kongress werden erste Daten vorliegen, wie gut sich Frauen auf diese Weise für einen HPV-Selbsttest motivieren lassen. Diese Daten können mit bereits vorhandenen Studien zum Einladungsmodell, z.B. der MARZY-Studie verglichen werden.

Conclusions: Um die Inzidenz des invasiven Zervixkarzinoms in Deutschland weiter zu senken, ist es essentiell, gezielte Strategien für Nicht-Teilnehmerinnen an der regulären Vorsorge zu entwickeln. Neben Einladungsverfahren ist die häusliche Selbstuntersuchung auf HPV eine vielversprechende Option. Die HaSCo-Studie wird von der Deutschen Krebshilfe unterstützt.

LW 03- Zervixkarzinomscreening in Deutschland und international - Teil B- Internationale Entwicklungen

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#3991

HPV-Impfung und Screening in Japan

40 - Public health

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Background/Objectives: Die Inzidenzrate für Gebärmutterhalskrebs in Japan beträgt 15,3 pro 100.000 Frauen. Das ist fast zweimal so hoch wie in anderen Hocheinkommensländer im asiatisch-pazifischen Raum und ebenfalls höher als in vielen Mittel- und Niedrigeinkommensländer. Besonders besorgniserregend ist dabei der starke Anstieg der Fallzahlen bei Frauen im gebärfähigen Alter. Der Hauptgrund dafür ist die geringe Vorsorge durch HPV-Impfungen sowie Gebärmutterhalskrebs-Screenings.

Methods: Die aktuellen Zervixkarzinom-Vorsorgerichtlinien in Japan empfehlen eine Vorsorgeuntersuchung alle zwei Jahre mittels Pap-Abstrich für Frauen ab 20 Jahren. Eine Altershöchstgrenze existiert zur Zeit nicht. Es gibt kein organisiertes Screeningprogramm wie z.B. im Grossbritanien, allerdings haben Frauen diverse Möglichkeiten ein Screening vornehmen zu lassen. Sie können sich im Rahmen eines Gesundheits-Check-ups am Arbeitsplatz, kommunaler Screeningprogramme oder beim Gynäkologen untersuchen lassen. In der Realität kommen Frauen mit der Zervix-Vorsorgeuntersuchung das erste Mal bei einer Schwangerschaft in Berührung und es passiert nicht selten, dass dann bei der Festellung ebendieser auch ein Gebärmutterhalskrebs entdeckt wird. 2020 wurden die Vorsorgerichtlinien zwar überarbeitet, aber es gilt weiterhin die Empfehlung alle zwei Jahre einen Pap-Abstrich durchzuführen, allerdings nur bis zu einem Alter von 65 Jahren. Ebenfalls wird Frauen im Alter zwischen 30-60 alle fünf Jahre die HPV-DNA-Diagnostik im Primärscreening empfohlen. Die Notwendigkeit einer HPV-DNA-Diagnose in Verbindung mit einer zytologischen Untersuchung in der Altersgruppe 30-60 wurde mit der Kategorie C als niedrig eingestuft - die Verfahren werden demnach nicht zur populationsbasierten Krebsvorsorge empfohlen. Ebenfalls wird von HPV-Selbsttests abgeraten. Momentan liegt die Vorsorgerate bei 30-40%.

Results: In Japan wurde der zweiwertige HPV-Impfstoff im Oktober 2009 lizenziert, der vierwertige HPV-Impfstoff im Juli 2011. Kurzzeitig, von 2010 bis 2012 wurden für den Einsatz des Impfstoffes bei Mädchen von 12-16 Jahren öffentliche Mittel zur Verfügung gestellt und ab April 2013 wurde der HPV-Impfstoff in das nationale Immunisierungsprogramm für Mädchen der o.g. Altersgruppe aufgenommen. Die anfängliche Impfabdeckung war mit 70-80% sehr hoch. Am 14. Juni 2013 jedoch, zwei Monate nach der formellen Aufnahme in das nationale Immunisierungsprogramm Japans wurden die aktiven Empfehlungen und Aufrufe zur HPV-Impfung im Zuge sensationsträchtiger Berichterstattungen in den Medien über unerwünschte Nebenwirkungen, die bisher in keinen kausalen Zusammenhang mit der Impfung gebracht werden konnten, zurückgezogen. Die Impfung blieb zwar weiterhin kostenlos für Mädchen von 12 bis 16 Jahren, aber die Kommunen und Ärzte durften die Impfung nicht mehr aktiv empfehlen. In der Folge fiel die Impfrate auf unter 1% und ist seither unverändert.

Conclusions: Im November 2021 kündigte das japanische Ministerium für Gesundheit, Arbeit und Wohlstand an, dass es wieder aktive Empfehlungen für den HPV-Impfstoff aussprechen werde, fast 9 Jahre nach der ursprünglichen Rücknahme von Empfehlungen. Ebenfalls angekündigt wurde, dass Nachholimpfungen angeboten würden für Frauen, die zwischen 1997 und 2005 geboren sind und sich bisher wegen Sicherheitsbedenken nicht haben impfen lassen. Aktuell schließt das japanische HPV-Impfprogramm sowohl die Verwendung des 9-fach Impfstoffs als auch Jungen von der Impfung aus.

CS04- Clinical applications for emerging sequencing technologies

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#4002

Genome-wide microRNA analysis to inform biomarker design

15 - Molecular markers

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Background/Objectives: MicroRNAs (miRNAs) are a class of small non-coding RNAs that have emerged as key regulators of gene expression. They are often found deregulated in cervical cancer and precancerous lesions and are increasingly recognized as promising biomarkers for cervical cancer diagnostics. Alongside altered expression in cervical (pre)cancer, miRNAs meet most of the requirements of being an ideal biomarker, such as their presence in small amounts of cervical specimens (i.e. tissues, scrapes, self-samples) and biofluids (i.e. blood, urine) allowing for relatively non-invasive sample collection. In addition, miRNAs are remarkably stable and can be assayed by a range of different methods. Next-generation sequencing is the preferred method for accurate and sensitive miRNA profiling, and as such numerous small RNA sequencing technologies have been developed. This has resulted in an explosion of biomarker studies and a comprehensive list of promising miRNAs for (cervical) cancer diagnostics.

Methods: ..

Results: ..

Conclusions: This presentation will give an overview of our expertise on genome-wide miRNA biomarker discovery for early detection of cervical cancer and summarizes recent findings on HPV-positive self-samples, HPV-immortalized cells and exosomes.

MSS07A- HPV screening - first experiences - Part 1) HPV screening in real life

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#3956

HPV primary screening: the Scottish approach

10 - HPV screening

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Background/Objectives: THis presentation will describe the introduction of HPV primary screening to the screening programme in Scotland, our unique experience to date and some early data on the effectiveness of the new primary test within a Scottish context.

Methods: The unique elements of the introduction of HPV primary screening will be described focussing on the IT challenges, procurement of the HPV platforms and the impact of the pandemic on the "go live" date and early months of the new service. Early data on the performance of the primary HPV test and the cytology triage will be presented. The programme uses focussed co-testing in a series of pathways designed to use cytology and HPV testing where it is deemed clinically appropriate

Results: The data so far has been difficult to compare with cytology as the primary test due to the disruption to the programme caused by the pandemic. However, early data suggests an increased detection of disease and less impact on colposcopy than the earlier modelling indicated. The re-designed laboratory service appears to be working well and data on the performance of both labs in HPV testing and cytology traiage will be presented.

Conclusions: Despite years of planning the impact of the pandemic provided a significant challenge to the introduction of HPV primary screening in the Scottish screening programme. The new service adapted well in the face of the issues the pandemic presented and due to the commitment of the staff across the programme the re-designed programme is now well established and has 2 years of data to analyse. The Scottish IT system is one of the strengths of the screening programme and has underpinned the move to HPV primary. The introduction of HPV primary screening in Scotland has several unique aspects and these will be descibed during this presentation.

HN06- HPV and H&N Forum - Immunologic considerations

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United States

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#3940

Defining HPV-specific B cell responses in head and neck cancer patients

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Tumours can harbour significant numbers of B cells and plasma cells, however, little is known about the antigen specificity of intra-tumoral B cells.

Methods: Using a wide range of methodologies including ELISPOT, flow cytometry, scRNAseq, and multiplex IHC, we characterized human papillomavirus (HPV)-specific B cell responses in the tumor microenvironment (TME) of HPV+ head and neck cancer patients.

Results: We show that HPV-specific B cell responses are detectable in HPV-positive head and neck cancers, with active production of HPV-specific IgG antibodies in situ. HPV-specific antibody secreting cells (ASCs) were readily detectable (~0.7-25% of IgG+ ASCs) in the TME with minimal bystander recruitment of influenza-specific cells, suggesting a localised and antigen-specific ASC response. HPV-specific ASC responses, which correlated with plasma IgG titres, were directed against the HPV proteins E2, E6, and E7, with E2-specific responses tending to be the most dominant. Using intra-tumoral B cells and plasma cells, we generated several HPV-specific human monoclonal antibodies, which exhibited a high degree of somatic hypermutation, consistent with chronic antigen exposure. scRNAseq analyses revealed the presence of activated B cells, germinal centre B cells, and ASCs within the TME. ASCs and B cells were preferentially localised in the tumour stroma, with well-formed clusters of activated B cells indicating ongoing germinal centre reactions.

Conclusions: Overall, we show that antigen-specific activated and germinal centre B cells as well as plasma cells can be found in the TME. Our findings provide a better understanding of humoral immune responses in human cancer and suggest that tumour-infiltrating B cells could be harnessed for the development of novel therapeutic agents.

LW 04- Differenzialdiagnostik bei auffälligem Screeningbefund

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#3955

HPV-TESTANFORDERUNGEN FÜR DAS ORGANISIERTE GEBÄRMUTTERHALSKREBS-SCREENING PROGRAMM IN DEUTSCHLAND

10 - HPV screening

Iftner T[1]

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Background/Objectives: Die Richtlinie für das organisierte Gebärmutterhalskrebs-Screening-Programm (oKFE) in Deutschland bietet Frauen ab einem Alter von 35 Jahren alle drei Jahre einen HPV-Test in Kombination mit einer Zytologie an. Frauen ab 20 Jahren bekommen weiterhin jährliche PAP-Abstriche und zwischen 30-35 Jahren einen HPV-Test als Triage. Ein HPV-DNA-Test im oKFE sollte nur die 13 HPV-Typen nachweisen, die von der IARC/WHO als krebserregend (class I/IIa) für den Menschen eingestuft wurden. Die klinische Sensitivität und Spezifität eines HPV-Tests für den Nachweis von CIN2+ darf nicht unter 95% bzw. 98% bereits etablierter und in RCTs verwendeter HPV-Testsysteme wie dem HC2-Test liegen. Außerdem sollte die Positivitäts-Rate bei Frauen mit unauffälliger Zytologie nicht höher sein als die des HC2-Tests. Die Reproduzierbarkeit innerhalb eines Labors und zwischen verschiedenen Laboren mit unterschiedlichen Geräten und Mitarbeitern sollte mindestens 90% betragen. Da die oKFE Screening-Intervalle von 3 Jahren vorsieht, sollte sich die longitudinale kumulative Inzidenzrate von CIN2+ und der negative Vorhersagewert (NPV; für mindestens 3 Jahre) nicht signifikant von dem Goldstandard HC2 unterscheiden. Darüber hinaus sollte der gewünschte Test in Populations-basierten Studien überzeugende Leistungen gezeigt haben, vom Labor und den überweisenden Gynäkologen akzeptiert werden und kosteneffektiv sein.

Methods: n.a.

Results: n.a.

Conclusions: n.a.

CS05- Applying Methylation assays for clinical use

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#3966

Use of methylation markers as guidance for CIN2/3 management

15 - Molecular markers

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Background/Objectives: Many CIN2/3 lesions, especially in young women of reproductive age, show spontaneous regression. Since surgical treatment is associated with cervical morbidity and preterm birth, overtreatment should be avoided. A test that can predict clinical regression of CIN2/3 lesions may help to prevent overtreatment and is urgently needed. Current histopathological grading of CIN by pathologists cannot discriminate between regressive and non-regressive CIN2 and CIN3. Several biomarkers have been evaluated for their prognostic value such as HPV viral load and immunohistochemical staining of p16INK4A and Ki-67, but none of these were able to predict regression or progression of CIN. Recent studies have shown that DNA methylation levels of host cell genes and viral genes increase with increasing severity of CIN grade and are extremely high in cervical cancer. DNA methylation has shown a high sensitivity for cervical cancer and advanced CIN2/3. In addition, a well-studied methylation marker panel consisting of host cell genes FAM19A4 and miR124-2 showed a similar reassurance against CIN3 and cervical cancer compared with cytology up to 14 years of follow-up. Based on these results, it is assumed that DNAmethylation detects CIN2/3 lesions at highest risk of progression to cervical cancer. To date, the prognostic value of two methylation biomarker panels have been evaluated as a predictor of clinical regression in women with untreated CIN2 or CIN3. The S5 classifier, which evaluates methylation of EPB41L3 and the late (L1 and/or L2) regions of HPV16, HPV18, HPV31, and HPV33, was able to predict regression or progression of CIN2 in women <27 years. Recently, the QIAsure Methylation Test ®, which evaluates methylation of FAM19A4/miR124-2, was studied in a prospective follow-up study of women aged 18 to 55 years with untreated CIN2 or CIN3. Women with a negative FAM19A4/miR124-2 result on the baseline clinician-collected cervical sample showed more clinical regression (74.7%) than women with a positive methylation result (51.4%, p=0.013). Similar findings were found for baseline self-collected samples. The use of methylation markers as guidance for CIN2/3 management will be further discussed in this presentation.

Methods: --

Results: --

Conclusions: --

MSS07B- HPV screening - first experiences - Part 2) HPV self-sampling: real life implementation experiences

Forslund Ola
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#3965

Self-sampling within routine cervical cancer screening in Region of Skåne, Sweden

10 - HPV screening

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Background/Objectives: Region Skåne is one of 21 regions in Sweden. The region has about 1.4 million inhabitants, and cervical cancer screening is organized by Public Health. About 400 000 women are in the screening ages between 23-70 years and all samples are analyzed at one laboratory. Year 2017 primary HPV screening (mRNA assay) was introduced for women 30-70 years old. Recently in September year 2021, vaginal self-sampling was commenced as the first sample option for women aged 23-70 years. The aim of the presentation is to give an overview of the characteristics and performance of the newly introduced self-sampling program.

Methods: Organization: The organization of the self-sample screening program will be described via interviews of key informant personnel at Laboratory Medicine Skåne. The qualitive performance of the self-sample program will be analyzed by the use of data from the cytology/pathology database. HPV testing: Self-sampling kits (Multitest Swab Specimen Collection kit, Hologic) are sent by mail to the women. The kit contains information along with the necessary equipment. The self-sample is returned in a prepaid envelope to the Department of Pathology in Lund. Self-samples are heated at 90°C for 1h and 15 min, and cooled to room temperature before being analysed by Aptima HPV mRNA. Self-samples with invalid results from the HPV mRNA assay are re-tested in duplicate and scored as valid if at least one of the results are valid. Self-sample-HPV-positive women are then invited for a follow-up within 3 months, where liquid based cytology (LBC) cervical samples are collected by midwifes. Renewed HPV analysis are performed and reflex cytology are made from HPV positive samples. Further gynaecological follow-up due to cytology of >ASCUS+ is done at outpatient colposcopy clinics, where appropriate histological specimens are taken and sent for pathological assessment at Department of Clinical Pathology in Lund. Non-attendees for the follow-up procedure with a midwife are sent a reminder by regular mail. Estimated costs for the self-sampling program will be compared to that of the previous primary HPV-screening approach of LBC samples. We will include costs from the laboratory and midwifes, such as cost for self-samples kits sent out by post, HPV-analyses, follow ups at midwifes of self-sample HPV-positive women with LBC-sampling and renewed HPV testing and reflex cytology.

Results: At the conference an overview of the organization of self-sample screening program will be described. In addition, the outcome of self-sampling program will be given as well as the estimated cost of the program.

Conclusions: Will be given at the conference.