EUROGIN 2022 ABSTRACTS

FREE COMMUNICATIONS SESSIONS

FC01 - Screening methods and triage 1

Qi Bingli
China

Liu Shikai
China

#3686

Management of Minimally Abnormal Cervical Cancer Screening Test Results by DNA Methylation Detection

24 - Risk management

Qi B[1], Miao Z[2], Liu S[1]

[1]Department of Gynecology and Obstetrics, Cangzhou Central Hospital, Cangzhou, China

[2]Department of Pathology, Cangzhou Central Hospital, Cangzhou, China

Background/Objectives: The ASCCP released consensus guidelines that formalized a strategy for management of cervical cancer based on estimates of underlying high-grade precancerous lesions or cancer (CIN3+). The remainder were minimal abnormalities including high-risk HPV (hrHPV; +)-cytology (-) and cytology (LSIL and ASCUS). Due to the great differences in cytological techniques, pathological CIN3 + missed diagnosis often occurs in minimally abnormal screening results, especially in areas with limited resources. The main purpose of this study is to find clinical evidence of methylated PAX1 and JAM3 genes in minimally abnormal cervical cancer screening test results, especially in ASCUS.

Methods: The subjects with minimally abnormal cervical cancer screening results were recruited in the Cangzhou central Hospital, China from 2019 to 2022. The inclusion criteria were female with age ≥20 and sexual experience. The exclusion criteria included: women had history of gynecological cancers, surgery of cervix and uterine body, or at pregnancy. The results of the methylated PAX1 and JAM3 genes (P&Jm) were determined by CisCer qPCR system (CISPOLY Co., Beijing, China). Positive rate, sensitivity, specificity, and accuracy for cytology, hrHPV and the methylation level of both genes were analyzed. Epida-ta3.1 was used for data entry and SPSSl8.0 software was used for statistical analysis.

Results: Total 1200 subjects were recruited and analyzed in the study. The results showed that the CIN2+ of patients with minimal abnormalities was higher than 5 %, especially in ASCUS group. The final diagnosis was confirmed by colposcopy or histology of colposcopy directed biopsy. The results showed that the combination of P&Jm genes was significantly higher in patients with minimal abnormalities in CIN3+ than those in CIN2, CIN1, and normal cervix (P<0.001). The sensitivity of P&Jm for CIN3+ were more than 75%, and the specificity and positive predictive rate were more than 90%, respectively. P&Jm still shows good results for clinical application on ASCUS and hrHPV triage in the study. P&Jm test reduces more than 20% colposcopy referral rate without cancer missed diagnosis than patients with minimally abnormal-HPV16/18 positive results. Compared the patients with minimal abnormalities with HPV16 / 18 (+) results, P&Jm detection can reduce the referral rate of colposcopy by more than 20%, and there is no missed diagnosis of cancer.

Conclusions: The current results show that the combined detection of methylated PAX1 and JAM3 genes is a promising triage biomarker for the patients with minimal abnormalities in the primary screening of cervical cancer in Chinese population. The single center clinical evidence can improve the clinical effectiveness and decrease the numbers of colposcopy and follow-up without cancer missed in the study.

Ikenberg Hans
Germany

Ikenberg Hans
Germany

#3617

COMPARISON OF THE GENIUSTM SYSTEM FOR DIGITAL CYTOLOGY WITH THE THINPREP® IMAGING SYSTEM

17 - Automation in cytology

Ikenberg H[1], Lieder S[2], Ahr A[1], Xhaja A[1]

[1]1Cytomol, Laboratory for Cytology and Molecular Biology, Frankfurt, Germany

[2]Hologic, Wiesbaden, Germany

Background/Objectives: Up to now the gold standard in cervical cytology was liquid based cytology (LBC) with computer-assistance (CAS). A further increase in sensitivity and specificity would be welcome especially as experience with abnormalities will decrease with increasing rates of HPV vaccination. A new approach is digital cytology (DC) with artificial intelligence (AI) which also allows assessment by external experts worldwide. We compared the two systems in a retrospective study.

Methods: 1994 ThinPrep® LBC slides (Hologic, Wiesbaden, Germany) pre-analyzed with the Imaging system (CAS) in routine cotesting cytology and HPV in 2020 were reviewed in a blinded fashion with the GeniusTM System for digital cytology (Hologic, Wiesbaden, Germany). In 555 cases, among them all >LSIL, a histology result was available. The slides were digitally scanned (volumetric scan) in 14 levels which were integrated to one. AI algorithms finally present a gallery of 6 "tiles" each in 5 categories. 6 additional "tile-rows" may be shown. Therefrom the diagnoses are made. If necessary, the digitalized full slide can be fully screened on the monitor. All cytotechnicians and cytologists had successfully attended a morphology training and had experience with over 10.000 DC cases when beginning the study. All cases with a mismatch between DC and Imaging system results were reviewed by an independent cytologist.

Results: Over 95% of the cases could be technically successful digitalized. The familiarization with the system was rapid, only the micrometer screw was sometimes missed. However, the acceptance of the presented "tiles" by the cytotechnicians was very high. In the retrospective analysis we found in 86,5% of the slides a complete match between both systems. Using the same cytology categories and considering the histology result the match was 90,37%. Applying in addition a cytology follow-up and/or a retrospective review it reached 97,34%. Only in 0,65% a major discrepancy (two grades of cytology or a LSIL / HSIL shift) was observed. All of them in favour of DC. The screening time was significantly shorter with DC.

Conclusions: With the GeniusTM system for digital cytology sensitivity and specificity for LSIL and HSIL are at least as high as with LBC and CAS. Screening time is significantly lower. The acceptance by cytotechnicienas and cytologists is high.

Giachini Claudia
Italy

Giachini* Claudia
Italy

#3689

Peer Review Cytology Plus (PRCP): a new software for the Internal Quality Control in cytology

21 - New technologies

Giachini* C[1], Pompeo G[1], Meoni M[1], Cannistrà' S[1], Paganini I[1], Di Stefano C[1], Sani C[1], Carozzi* F[1], Matucci* M[1]

[1]Regional Cancer Prevention Laboratory - Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

Background/Objectives: * These authors contributed equally. Peer Review is an internal quality control (IQC) system used in the laboratory of ISPRO (Institute for Cancer Research, Prevention, and Clinical Network) - where about 60,000 Pap tests from all over Tuscany are performed annually. It consists of the daily examination, by all cytologists of the lab, of cervical smears judged abnormal or of difficult interpretation, which emerge routinely. The examination is performed blindly, without opinion exchanges, and each cytologist records his/her own evaluation. Smears are then collegially discussed and reviewed using a multi-head microscope and a consensus on the final diagnosis (FD) is reached; FD generally corresponds to the majority diagnosis (MD). The aim of the study was the implementation of software, called Peer Review Cytology Plus (PRCP), designed to simplify ICQ data recording and statistical analysis aimed to improve the evaluation of the laboratory performance.

Methods: Software design has been driven by the non-computerized procedure with which peer review has always been performed in our laboratory since 1989 (1,2). The main goal was to achieve the following aims: - to simplify the recording of data of the peer review process by each cytologist, which was previously done without computerized tools - to generate a report for each smear with the following elements: the majority diagnosis (MD), automatically calculated; an histogram showing the distribution of the results recorded by each reader; the final and histological diagnosis (HD). - to generate a report for statistical analysis aimed to evaluate: i) the participation (%) of each reader to the peer review sessions; ii) the level of concordance of each cytologist with MD, FD and HD; iii) the level of agreement among readers.

Results: The Peer Review Cytology Plus (PRCP) has already been successfully introduced in our laboratory; some features are currently being implemented and validated such as the report showing the level of concordance of each cytologist with MD, FD and HD and the level of agreement among readers. Among the advantages of the introduction of this computerized tool are the complete traceability of all cases sent for peer review and the possibility of carrying out statistical analysis to evaluate the performance of each cytologist and of the whole laboratory. Moreover, this software allows comparing the diagnosis distribution of different smears from the same patient (for example baseline vs follow-up) as well as the revision of smears whose cytological and histological results were discordant.

Conclusions: The Peer review procedure represents an important method of IQC; the continuous on-going discussion of positive and difficult patterns among cytologists with different levels of experience should result in an improvement in the uniformity of reading and, consequently, in the achievement of optimal values of reproducibility, as well as improving levels of diagnostic accuracy. The Peer Review Cytology Plus (PRCP) software represents a very important evolution allowing the reduction of time-consuming for the daily IQC - thought the facilitation of the peer review process - and the strictly monitoring of the laboratory performances in terms of inter-observer agreement, reproducibility and functioning of the whole laboratory.

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Downham Laura
France

Downham Laura
France

#3117

Performance of oncoprotein-based tests to detect CIN2+ for cervical cancer screening and triage: a systematic literature review

10 - HPV screening

Downham L[1], Rol M[1], Ramirez T[1], Valls J[1], Gunter M[3], Almonte M[1]

[1]Early Detection, Prevention and Infections branch, International Agency for Research on Cancer, Lyon, France

[2]Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium

[3]Nutrition and Metabolism branch, International Agency for Research on Cancer, Lyon, France

Background/Objectives: WHO current guidelines recommend using DNA HPV detection rather than cytology in primary screening and treatment approaches for cervical cancer. HPV testing has high sensitivity but moderate specificity to detect cervical intraepithelial neoplasia lesions 2 or greater (CIN2+). Therefore, accurate triage tests are needed to identify women at high risk of CIN2+. The HPV viral oncoproteins E6 and E7 are necessary for oncogenic transformation and are overexpressed during cervical carcinogenesis. The detection of these proteins are promising candidate markers for screening or triage. Objective: To provide an up-to-date systematic literature review of the clinical performance of oncoprotein-based HPV tests to detect CIN2+ and CIN3+ lesions for cervical cancer screening and triage.

Methods: A systematic literature search of PubMed, Embase and Web of Science was conducted. Studies reporting original data on the sensitivity and specificity of oncoprotein-based HPV tests for cervical cancer primary screening or triage in women aged 18+ were included. Histologically confirmed CIN2+ or CIN3+ were considered as the gold standard. A meta-analysis using mixed effects logistic regression models was performed to obtain heterogeneity-adjusted sensitivity and specificity estimates.

Results: Twenty-three studies were included in the analysis, the majority being obervational studies (96%) and conducted in Asia (44%). Seventeen studies (74%) reported the performance of oncoprotein-based tests in screening settings while 6 studies (26%) in triage settings. Eighteen studies (78%) targeted the viral oncoprotein E6 alone and mean age was above 50 years old for most of the studies (74%). Sensitivity for CIN3+ and specificity (excluding CIN2) varied across studies (ranges 37.8%-100.0% and 67.9%-100.0% respectively) in screening settings, resulting in pooled estimates of 58.1% (95%CI 44.1-70.8) for sensitivity and 98.7% (95%CI 98.0-99.2) for specificity. Sensitivity and specificity for CIN2+ were 45.1% (95%CI 29.0-62.2) and 98.7% (95%Ci 98.0-99.2) respectively. In a triage setting, the sensitivity for CIN3+ was higher (69.0%, 95% CI 57.6-78.4) and the specificity slightly lower (95.7%, 95% CI 90.8-98.0). The same pattern was observed for CIN2+ with a sensitivity of 58.2% (95%CI 50.5-65.5) and a specificity of 92.3% (95%CI 85.1-96.2).

Conclusions: These preliminary results show that oncoprotein-based HPV tests have better performance in triage than in screening settings, although a high heterogeneity was observed across studies, which could be due to the test target (different HPV types and oncoproteins), the sample collection method (collected by a clinician or self-collected), device (endocervical brush, cervical brush), or medium (Swab or PreservCyt). These factors will be further investigated and a study-quality assessment will be conducted.

Pompeo Giampaolo
Italy

Pompeo Giampaolo
Italy

#3182

Implementation of a centralized HPV-based cervical cancer screening programme in Tuscany: first round results and comparison with the foregoing Pap-based screening programme

10 - HPV screening

Carozzi F[1], Burroni E[1], Confortini M[1], Pompeo G[1], Bisanzi S[1], Cellai F[1], Paganini I[1], Mantellini P[1], Iossa A[1], Lelli L[1], Di Pierro C[1], Matucci M[1], Cannistrà S[1], Rosati R[3], Mongia A[2], Visioli C[1], Gorini G[1], Sani C[1]

[1]ISPRO, Florence, Italy

[2]Careggi University Hospital, Florence, Italy

[3]Southeast Tuscany Local Health – Grosseto Hospital, Grosseto , Grosseto, Italy

Background/Objectives: In Tuscany region HPV-based cervical cancer screening programme is ongoing from 2013, with a strong level of centralization towards the Regional Laboratory for Cancer Prevention of ISPRO institute (Florence). Aims of this study were to evaluate the performance of the first round of HPV-based screening and to compare it with the previous round of Pap-based screening.

Methods: The transition from Pap to HPV-based screening started gradually in 2013 from older women and from 3 out of 12 Tuscany Local Health Units (LHUs). Data from Florence and Grosseto LHUs (about 300,000 women) were analysed and performance screening indicators were estimated.

Results: HPV-based indicators recorded a good performance, with an increased compliance vs. Pap-based programme. We registered a substantial decrease of waiting times from sampling to test reporting, probably related to the centralization strategy. Since the screening protocol was the same and since the samples were analyzed in a unique regional laboratory, we could hypothesize that the different HPV positivity (6.8% in Florence vs 8.4% in Grosseto) was due to real difference in the HPV prevalence among women of the two LHUs. HPV-based programme led to an important increase of colposcopy referral rate (4.3% vs. 1.2%) and to a significant increase of about three-fold of CIN2+ DR (8.3‰ vs. 3.4‰). The difference of the CIN2+ DR between traditional Pap test and HPV+/triage Pap test registered at baseline (respectively, 3.4‰ vs. 5.8‰ for Florence and 3.6‰ vs. 6.2‰ for Grosseto) was due to a better performance of the Pap test of triage in comparison with the Pap test as primary test.

Conclusions: The transition phase carried out in Tuscany region from Pap to HPV-based screening was well planned and the choice to introduce a strong centralization towards a unique laboratory with a long experience in this specific field, determined a higher efficiency of the screening process. Our data confirmed that HPV-based is more effective in detecting high-grade precancerous and cancerous lesions than Pap-based screening and it is characterized by an "anticipatory effect" in the detection of CIN2+ lesions. Referral to colposcopy, as expected in a prevalence round, increased significantly; thus, screening programmes that decided to move from Pap-based to HPV-based screening, should include increased resources dedicated to colposcopy services. Therefore, the management of women with a positive HPV test in successive HPV-based rounds that were negative in the previous HPV round could probably be different, since this population is characterized by a lower risk to develop a CIN2+ lesion because they are women with a recent HPV infection. Thus it is strongly necessary to start thinking how the current screening protocol could be modified in the subsequent screening rounds (incidence round), in order to reduce the risk of unnecessary colposcopy and treatments.

Forslund Ola
Sweden

Forslund Ola
Sweden

#3612

Co-testing in cervical screening among 40-42 year old women is unreasonable

10 - HPV screening

Forslund O[1], Borgfeldt C[1], Leksell A[2]

[1]Lund University, Lund, Sweden

[2]Laboratory Medicine, Lund, Sweden

Background/Objectives: The screening program for cervical cancer in Sweden, recommends use of primary HPV screening for women > 30 years to 65 years. Co-testing with both HPV-analysis and cytology is recommended at the first screening after the age of 40. In order to fulfil co-testing, all screening women within the Region of Skåne at the age of 40-42 years were co-tested. The aim of the audit was to investigate the proportion of severe dysplasia as diagnosed by cytology and histological follow up among women with Aptima HPV negative tests. Also, the cost of the added co-testing cytology to the HPV primary screening program was calculated.

Methods: The local cytology registry was used to identify 40-42 year old women who attended screening and were co-tested during 4 years from January 2017 to December 2020. The Aptima HPV mRNA assay detects 14 HPV types and for Aptima HPV negative women with high-grade cytology or histological HSIL we performed extended HPV typing, for 40 HPV types, by the use of PCR using modified GP5+/6+ (MGP) primers followed by a Luminex assay. To estimate the added cost of cytology to identify each histology confirmed cervical HSIL case among Aptima HPV negative women, we used the current cost of EUR 21.2 per cytology evaluation at our laboratory.

Results: Out of 19,599 women, 5.8% (1137/19,599) had abnormal cytology. Among Aptima HPV negative women, 0.11‰ (2/18,132) had histologically confirmed HSIL. One of the women was infected with HPV18 and the other with HPV73 at the diagnosis of HSIL. The calculated cost to find one HSIL, via adding cytology to HPV negative cases, was approximately EUR 200,000.

Conclusions: The clinical benefit of a single co-test of cytology at 40-42 years added to an HPV-based screening program appears hesitant and economically unreasonable.

Rebolj Matejka
United Kingdom

Rebolj Matejka
United Kingdom

#3554

CYTOLOGY INTERPRETATION AFTER A CHANGE TO HUMAN PAPILLOMAVIRUS TESTING IN PRIMARY CERVICAL SCREENING: EVIDENCE FROM THE ENGLISH PILOT

10 - HPV screening

Rebolj M[1], Mathews C[1], Denton K[2]

[1]King's College London, Faculty of Life Sciences , London, United kingdom
[2]North Bristol NHS Trust, Southmead Hospital, Severn Pathology, Bristol, United kingdom

Background/Objectives: Overcalling of abnormalities and excess colposcopy referral of women without high-grade cervical intraepithelial neoplasia (CIN2+) have been major concerns for using cytology triage in women with positive high-risk human papillomavirus (HPV) tests. Previous studies comparing cytology evaluation with and without the knowledge of a positive HPV test tended to be small and used archived material, whereby any cytological abnormalities detected after a positive HPV test had been revealed did not affect the women's clinical management. We investigated the effect of revealing HPV positivity on cytological interpretation in the English HPV pilot study.

Methods: The pilot compared the routine implementation of primary cervical screening based on cytology, where HPV test results were not available prior to cytology reporting, with that based on HPV testing, where cytology was only required after positive HPV tests. Women were managed according to the results of the relevant screening and triage tests. We studied the proportions of women aged 24-64 referred to colposcopy directly (after abnormal cytology in the screening sample) vs. after early recalls at 12 and 24 months (after negative cytology in the screening sample but persistent HPV positivity), the detection of CIN2+, and the positive predictive value (PPV) of colposcopy for CIN2+.

Results: We included 931,539 women screened with cytology and 403,269 screened with HPV testing. Revealed HPV positivity was associated with a higher direct referral to colposcopy after any abnormality, ORadj: 1.16 (95% CI: 1.14-1.18), and was higher for women with borderline changes (ORadj: 1.35, 95% CI: 1.30-1.40). Laboratories with higher direct referral referred fewer persistently HPV-positive women after the early recall. The detection of CIN2+ after direct referral increased with an ORadj of 1.17 (95% CI: 1.13-1.20) for informed vs. uninformed cytology; the detection after borderline changes increased with an ORadj of 1.39 (95% CI: 1.28-1.51). For most age groups and grades of cytological abnormality, the PPV for CIN2+ remained comparable under both conditions of interpreting cytology. In women aged 50-64 with high-grade dyskaryosis, however, the PPV increased from 71% to 83% after revealing HPV positivity, ORadj: 2.05 (95% CI: 1.43-2.93).

Conclusions: Quality-controlled cervical screening programmes can avoid inappropriate overgrading of HPV-positive cytology.

Pedersen Helle
Denmark

Pedersen Helle
Denmark

#3610

CAN HPV GENOTYPING AND CYTOLOGY TRIAGE FACILITATE HPV SCREENING OF YOUNG WOMEN 23-29 YEARS OLD?

10 - HPV screening

Pedersen H[1], Tønnes Pedersen B[1], Korsgaard Andreasen E[1], Bonde J[1]

[1]Molecular Pathology, Dept. Pathology, AHH-Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark

Background/Objectives: Primary HPV screening of young women have been advised against on the premise that the high HPV prevalence in this group would lead to unnecessary referrals and treatment. The advent of the childhood HPV vaccinated women in the screening program combined with new molecular approaches to HPV screening could change this dynamic in favor of HPV screening over the current cytology screening offer. Here we present HPV prevalence and genotype frequencies in women age 23-29 attending the organized cervical cancer screening program in Denmark. The data is used to model referral outcomes using HPV screening with HPV genotype and cytology triage as currently used in Denmark for women age 30-59 year.

Methods: 1000 SurePath cervical samples from women age 23-29 attending the cervical cancer screening program in the Capital Region of Denmark were randomly collected in Q3, 2021, tested by the BD Onclarity HPV assay, and combined with routine cytology outcomes retrieved from the National Pathology Database. Referral rates for the 23-29 years old were modelled upon the Danish algorithm for primary HPV screening for women 30-59 years old. Here, HPV positive w. HSIL/AGC/ASC-H/AIS and HPV positive w. ASCUS/LSIL and either of HPV16, 18, 31, 33, 52 are referred to colposcopy. HPV positive w. ASCUS/LSIL and either of HPV35, 39, 45, 51, 56, 58, 66 or 68 as well as HPV positive w. normal cytology independent of genotype are referred to re-test in 12 months. All HPV negative are returned to next screening round. The study is a quality development study approved by AHH-Hvidovre Hospital.

Results: Overall HPV positivity was 25% (N=252) for women age 23-29. Genotypes ranked by frequency was HPV18 (0.8%), HPV16 (2%), HPV31 (5%), HPV45 (6%), HPV33/58 (15%), HPV51 (16%), HPV52 (25%), HPV35/39/68 (32%), and HPV56/59/66 (35%). Overall, 3.5 % were HPV positive≥HSIL (N=16) or ASCUS/LSIL and either HPV16, 18, 31, 33, 52 (N=19); 1.5% were HPV positive w. ASCUS/LSIL and either HPV35, 39, 45, 51, 56, 66, 68 (N=15), and 20% (N=201) had normal triage cytology independent of genotype. One sample was invalid. Applying the described algorithm, direct referral rate to colposcopy amongst the 23-29 years would be 3.5% compared to 1.9% with the current cytology algorithm for this age group. Overall, 4.3% of all tested would be referred to a re-test in 6 months with the cytology algorithm.

Conclusions: HPV16 and 18 is close to be eradicated amongst 23-29 year old women, and the majority of HPV positive screening findings are one or more of HPV 35,39,56,59,66 and 68, generally considered so low in oncogenic potential that they do not merit immediate follow-up. Compared to current cytology screening, we conclude that difference in referral rate is limited when utilizing a HPV screening with genotyping and cytology triage and thus could make primary HPV screening feasible for women age 23-29 year offering the general benefit of improved CIN2/3 detection by HPV screening over cytology also for this age group.

Armaroli Paola
Italy
Armaroli Paola
Italy

#3733

Results after two screening rounds for primary HPV screening for cervical cancer, in a population based organized screening program in Piedmont, Italy

10 - HPV screening

Rizzolo R[1], Ronco G[1], Gillio-tos A[2], De Marco L[2], Cristina S[3], Valentini S[3], Larato C[1], Massari L[1], Leo L[1], Giordano L[1]

[1]Centre for Cancer Prevention, AOU Città della Salute e della Scienza, Torino, Italy, Turin, Italy
[2]Centro Unificato Screening Cervico-vaginale, AOU Città della Salute e della Scienza, Turin, Italy
[3]Pathology Unit, S.S. Trinità Hospital ASL NO, Borgomanero, Italy

Background/Objectives: In Piedmont Region, Italy, cervical cancer screening has been conducted with a primary high-risk human papillomavirus (hrHPV) test and cytology triage since February 2014. We here compare HPV positivity, colposcopy referral, and detection of cervical intraepithelial neoplasia (CIN) 2+ at first and at second screening round.

Methods: Within the organised population based screening programme, women of 30-64 years of age were randomised for invitation to a first screening round with hrHPV test in 2014-2015. They were invited for a second screening round in 2019-2020. The primary hrHPV test used was Hybrid Capture 2. hrHPV-negative women were scheduled for re-screening after 5 years. Women with a positive hrHPV (HPV+) test and cytology triage >= than ASC-US or unsatisfactory were directly referred to colposcopy, whereas HPV+ women with a negative cytology triage were re-invited for a hrHPV test after 1 year. If retesting was still positive they were referred to colposcopy, otherwise were scheduled for re-screening after 5 years

Results: In 2019-2020, 44162 women aged 30-64 were invited for the second screening round with hrHPV test, and 28552 participated (participation rate 65% vs 55% at first round, Relative Risk -RR- 1.17, 95%IC 1.15-1.18). At the second round, the observed positivity rate was 5.7%, compared with 7.6% at the first one (RR 0.74, 95%IC 0.70-0.78), and 344 women were immediately referred to colposcopy (1.2% compared with 1.5% at first round, RR 0.82, 95%IC 0.72-0.92). Compliance to colposcopy was 92%, not different from the one observed at the first round (93%). Immediate detection of CIN2+ lesions was 1.7‰, compared with 4.1‰ at the first round (RR 0.41, 95%IC 0.30-0.56). At hrHPV test repetition after 1 year, at second round 37% had a HPV+ result and were referred to colposcopy, compared to 53% at the first one (RR 0.70, 95%IC 0.60-0.81), but only the 40% (501) of the women negative at cytological triage could perform a hrHPV test after 1 year, due to the reduction of the screening activity during the COVID-19 emergency.

Conclusions: Among women at second screening round we observed a significantly higher participation, and significant reduction in the positivity rate (26%), in the immediate colposcopy referral rate (21%), and in the immediate CIN2+ detection (59%). Due to the COVID-19 emergency, data on HPV retesting at 1 year are not conclusive, but preliminary results would suggest an overall reduction in colposcopy referral and detection of CIN2+ lesions

Vaughan Laurence
United States

Vaughan Laurence
United States

#3542

RISK STRATIFICATION OF HPV-POSITIVE WOMEN USING EXTENDED GENOTYPING AND CYTOLOGY - RESULTS FROM THE BASELINE ONCLARITY TRIAL

12 - Triage of HPV positive women

Vaughan L[1], Gary D[1], Parvu V[1], Andrews J[1]

[1]Becton Dickinson and Company, Integrated Diagnostic Solutions, Sparks, United states

Background/Objectives: HPV screening is more sensitive than cytology but lacks specificity. Most cervical cancer screening programs triage women using HPV and cytology. The risk profiles of high-risk HPV types are very different, with seven 9-valent vaccine high-risk types contributing approximately 90% of all disease. Here we evaluate the ability of extended genotyping (beyond HPV 16/18) in combination with cytology to refer women to colposcopy.

Methods: We analyzed baseline data from the previously reported BD Onclarity PMA trial (1). Individual genotypes HPV16/HPV18/HPV/31/HPV45/HPV51 and three grouped types HPV33_58 / HPV35_39_68 / HPV56_59_66) were combined with cytology classifications (NILM, ASC-US/LSIL, High-grade) to generate hierarchical risk strata for CIN2+ and CIN3+ disease and to refer women to colposcopy. Baseline HPV, cytology and histology information was used to generate Receiving-Operator-Characteristic (ROC) curves of Sensitivity versus 1-Specificity, and CIN2+ and CIN3+ risk profiles. Different colposcopy referral strategies were then compared using tiered risk profiles generated by HPV genotype and or cytology category. We also compared performance to that of the similarly designed dual stain [CINtec PLUS / dual stain (DS)] Roche IMPACT PMA trial (2)

Results: Tiered hierarchical groupings (in descending risk order) of HPV 16, HPV 18/31, HPV 52/33_58, and HPV45/HPV51/HPV35_39_68/HPV56_59_66 resulted in stepwise reduction in both CIN2+ and CIN3+ baseline risk across High-grade, ASC-US/LSIL, and normal cytology categories. CIN2+ and CIN3+ ROC curves of xGT + cytology triage options were similar. Cytology performance in both the Onclarity and IMPACT trials was less sensitive and less specific than extended genotyping options. Previously published DS triage with HPV16/18 genotyping performance mapped closely to both CIN2+ and CIN3+ ROC curves and fell between ASC-US/LSIL HPV33_58/HPV45/HPV52 and NILM/ HPV33_58/HPV45/HPV52 extended genotyping options (Table 1).

Conclusions: Hierarchical extended genotyping risk groupings effectively triage patient risk, independent of cytology classification, and facilitates clinical action thresholds for colposcopy referral. When combined with cytology, extended genotyping offers the potential for improving triage of HPV+ women. Data from the BD Onclarity trial suggests that it outperforms cytology triage and may perform similarly to CINtec PLUS/dual stain triage using HPV16/18 genotyping. The implications for national screening programs are discussed. These findings warrant confirmation in head-to-head studies.

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laurence vaughan

Inturrisi Federica
Netherlands
Inturrisi Federica
Netherlands

#3607

FOURTEEN-YEAR RISK OF CERVICAL PRECANCER IN HPV-NEGATIVE WOMEN, STRATIFIED FOR PREVIOUS HPV AND CYTOLOGY RESULTS

24 - Risk management

Inturrisi F[1], Rozendaal L[2], Heideman D[2], Meijer C[2], Berkhof J[1]

[1]Epidemiology and Data Science, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

[2]Pathology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Background/Objectives: HPV-based screening programs still use one-size-fits-all protocols but efficiency and efficacy of programs may be improved by stratifying women based on previous screening results.

Methods: We collected 19 years of follow-up of women aged 29-61 from the POBASCAM HPV trial who received cytology and HPV co-testing at enrolment and after 5 years (blind HPV at enrolment in the control group). We selected 18,448 women who tested HPV-negative at 5 years and stratified them according to the preceding HPV and cytology results. We excluded women with a CIN2+ or hysterectomy between enrolment and 5 years. For each subgroup, we calculated 14-year CIN3+ and CIN2+ risk by Kaplan Meier method. Relative risks (RR) were calculated with a HPV-negative test as reference category.

Results: HPV-negative women had a 14-year CIN3+ risk of 0.48% (95% confidence interval (CI) 0.37-0.62). The CIN3+ risk among HPV-negative women was decreased in women who in the previous round had a negative HPV test (relative risk 0.90, 95% CI 0.81-0.99) or a negative co-test (0.90, 0.80-1.00) and markedly increased in women who in the previous round had a positive HPV test (4.92, 2.62-9.21) or a positive co-test (3.50, 1.93-6.36). The CIN3+ risk was not influenced by the previous cytology result. The CIN3+ risk among HPV-negative women was increased after both a previous HPV16-positive test (8.13, 3.15-20.96) and a previous HPV-positive/HPV16-negative test (3.98, 1.67-9.49). For end-point CIN2+, findings were similar except that the CIN2+ risk was increased after previous abnormal cytology (3.47, 2.01-5.99).

Conclusions: Long-term risk of CIN3+ among HPV-negative women were very low when there was no positive HPV test result in the previous screening round 5 years earlier, indicating that HPV results from multiple screens could be used for risk-stratification.

Figure 1. Cumulative risk of CIN3+ and CIN2+ in HPV-negative women per preceding test results after three screening rounds (14 years).

Sørbye Sveinung
Norway

Sorbye Sveinung
Norway

#3615

7-TYPE HPV MRNA TEST IN TRIAGE OF HPV DNA POSITIVE WOMEN

12 - Triage of HPV positive women

Sorbye S[1], Falang B[2], Antonsen M[1]

[1]University Hospital of North Norway, Tromso, Norway

[2]PreTect AS, Klokkarstua, Norway

Background/Objectives: In 2019, Norway implemented HPV DNA testing as a more sensitive method in primary screening for women 34-69 years of age. Reflex cytology was applied as triage of the screen positives in line with common international practice. Based on the known limitations and the effect of subjectivity for cytology interpretation, cytology has shown limited specificity in triage. This challenges the advantages of HPV primary screening by lowering the sensitivity. The search for improved triage alternatives is among the key priorities for the HPV expert community to improve diagnostic accuracy, allocate resources and reduce potential harm from over-treatment. We studied the performance of a 7-type HPV mRNA test in triage of HPV DNA positive women compared to cytology as the established reference method.

Methods: Since 2019 to date, the Department of Clinical Pathology, University Hospital of North Norway, has been using the HPV DNA test Roche Cobas 4800 in primary screening of women 34-69 years. All HPV DNA positives were evaluated by cervical cytology and a 7-type HPV mRNA test (PreTect HPV-Proofer'7, identifying mRNA E6/E7 from the genotypes 16, 18, 31, 33, 45, 52 and 58). According to national guidelines, follow-up was based on cytology. Histologically confirmed CIN2+ was used as the study endpoint.

Results: A total of 16,729 women were screened by HPV DNA testing. The positivity rate was 5.0% (836/16,729). During follow-up through end of November 2021, a biopsy has been taken from 31.1% (260/836) where the detection rate of CIN2+ among the HPV DNA positives was 8.7% (73/836). In triage of the HPV DNA positive women, 55.0% (460/836) had abnormal cytology (ASC-US+) and 36.5% (305/836) had positive HPV mRNA test. The sensitivity, specificity, PPV and NPV for the detection of CIN2+ were 76.7%, 47.2%*, 12.2%** and 95.5% by cytology and 80.8%, 67.8%*, 19.3%** and 97.4% for the HPV mRNA test respectively (*p<0.01, **p<0.01).

Conclusions: The 7-type HPV mRNA test had higher sensitivity, statistically significant higher specificity, PPV, and lower positivity rate than cytology in triage of HPV DNA positive women. A low positivity rate translates into a low referral rate for colposcopy, which is very appealing for triage situations to minimize the burden on the health care system. Women with a negative triage test can be followed up with repeat HPV DNA testing after 1-2 years. Molecular triage by mRNA is applicable for self-collected samples, an approach with clear benefits made even more important during COVID-19 and its impact on health care and cancer services to increase screening participation and prevention of cervical cancer.

Gottschlich Anna
Canada
Gottschlich Anna
Canada

#3640

PRELIMINARY RESULTS FROM A PRAGMATIC SEQUENTIAL RANDOMIZED TRIAL ON INTEGRATED CERVICAL CANCER SCREENING IN MAYUGE DISTRICT UGANDA (ASPIRE MAYUGE)

10 - HPV screening

Gottschlich A[1,2], Payne B[1,2], Trawin J[1,2], Albert A[1,2], Mitchell-foster S[3], Rawat A[2], Mithani N[1], Namogusa R[4], Pedersen H[1,2], Orem J[4], Smith L[1,5], Nakisige C[4], Ogilvie G[1,2]

[1]BC Women's Hospital and Health Service, Women's Health Research Institute, Vancouver, Canada

[2]University of British Columbia, Faculty of Medicine, Vancouver, Canada

[3]University of Northern British Columbia, Prince george, Canada

[4]Uganda Cancer Institute, Kampala, Uganda

[5]BC Cancer Agency, Cancer Control Research, Vancouver, Canada

Background/Objectives: Approximately 87% of cervical cancer diagnoses and 90% of cervical cancer deaths occur in developing regions, particularly in Sub-Saharan Africa, where there is often an absence or poor uptake of comprehensive screening programs. In Uganda, barriers to implementation of effective screening programs include poor health infrastructure and lack of human resources. Self-collection testing for the human papillomavirus (HPV), the primary cause of cervical cancer, may alleviate these barriers and has been shown to be feasible and acceptable among diverse populations. However, knowledge gaps persist in how to best implement self-collection HPV testing within community-based health services.

Methods: The aim of the Advances in Screening and Prevention in Reproductive Cancers (ASPIRE Mayuge) pragmatic sequential randomized trial was to compare the effectiveness of two cervical cancer screening models for self-collected HPV testing: Arm 1) community health worker recruitment (door-to-door) and Arm 2) invitation to community health meetings. Participants ages 25-49 from 31 villages in the Mayuge district of Eastern Uganda were enrolled from 2019-2021 and randomized to Arm 1 (Screening at home, N=1055) or Arm 2 (Screening at the health meeting, N=964) by clusters (villages). Participants completed surveys and were offered self-collection HPV testing. HPV results were returned to participants and those who were HPV positive were referred to a local health clinic for visual inspection with acetic acid (VIA) and thermal ablation. The primary outcome was attendance for follow-up VIA at a designated health clinic when indicated among all participants based on intention to treat. This outcome was compared between arms by estimating a mixed effect logistic regression model with cluster as a random intercept and adjusted for all known confounders at the individual and cluster level.

Results: In Arm 1 and Arm 2, 28.1% (N=296) and 24.9% (240) were HPV positive, and 22.0% (N=232) and 16.6% (N=160) of participants attended VIA, respectively. After adjustment for age, education, and number of living children, the model gave results suggesting that Arm 2 participants were less likely than Arm 1 to attend VIA (OR = 0.71, 95% CI: 0.56-0.90, p = 0.004).

Conclusions: In this population, participants who were recruited by community health workers in their homes were more likely to attend follow-up VIA. It is important to note that Arm 1 occurred before the COVID-19 pandemic, while Arm 2 occurred during the pandemic. Effects of the pandemic could confound the relationship between arm and attendance, but we unfortunately have no way of assessing the level of potential confounding. This study provides evidence that door-to-door recruitment by community health workers may be an effective method for implementing self-collection HPV testing in settings where cervical cancer screening is strongly needed.

FC03 - Vaccines 1

De Lepper Marion
Germany

De Lepper Marion
Germany

#3408

EFFECT OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION ON OCCURRENCE OF SUBSEQUENT ANOGENITAL WARTS (AGWs) IN PATIENTS WITH CURRENT OR HISTORY OF AGWs WORLDWIDE: A SYSTEMATIC REVIEW AND META-ANALYSIS

06 - HPV prophylactic vaccines

[1]Student in MSc Epidemiology by Distant Learning, London School of Hygiene and Tropical Medicine, London, United kingdom
[2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United kingdom

Background/Objectives: Anogenital warts (AGWs) are responsible for a high burden of disease and are caused mainly by the low-risk human papillomavirus (HPV) types 6 and 11. After standard therapy up to approximately 48.5% of patients suffer from re-detection of AGWs. The aim of this systematic review was to evaluate whether prophylactic HPV vaccination reduced the risk of subsequent AGW occurrence in patients with current or history of AGWs.

Methods: A literature search was carried out on June 30, 2021 in PubMed, MEDLINE, EMBASE, Global Health, Scopus, and the Cochrane library. Randomised trials and analytical observational studies on patients with clinically diagnosed history or current AGWs worldwide were included. Studies on patients only diagnosed by laboratory tests were excluded. Studies were included when they used HPV vaccines covering at least HPV type 6 and/or 11. The primary outcome for the randomised trials was the proportion of AGW re-detection after HPV vaccination in patients with previously clinically diagnosed AGWs. The calculated risk ratio (RR) of those studies were summarised in a meta-analysis. A sensitivity analysis was conducted, excluding the study that mostly differed regarding study design and study population. The observational studies were evaluated narratively. Finally, quality assessment of the included studies and assessment for publication bias were conducted.

Results: Totally, six studies were included in the systematic review, four randomised trials and two observational studies. The effect of HPV vaccination on subsequent AGWs among patients with current AGWs which received AGW therapy was investigated in randomised trials, while the association between HPV vaccination and subsequent AGWs among patients with AGW history either cleared naturally or after treatment was investigated in observational studies. The summary RR of the randomised trials showed evidence of a risk reduction in subsequent occurrence of AGWs in patients with HPV vaccination compared to controls among patients with previous AGWs (RR = 0.56, 95% confidence interval (CI): 0.33 - 0.95). A sensitivity analysis resulted in RR = 0.46 (95% CI: 0.33 - 0.64), indicating a robust result. We did not carry out a meta-analysis on included observational studies due to the limited number of similar studies. Most observational studies reported a lower risk of subsequent AGWs among HPV vaccinated people compared to controls among patients with AGWs.

Conclusions: The systematic review showed some evidence that HPV 6 and/or 11 targeted vaccination reduced the risk of subsequent AGW occurrence among patients with previous AGWs. More studies may validate this result.

Sparen Par
Sweden

Sparén Par
Sweden

#3767

Quadrivalent HPV vaccination and long-term risk of adverse pregnancy outcomes

06 - HPV prophylactic vaccines

Lei J[1], Sparén P[1]

[1]Dept. of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Background/Objectives: Current available HPV vaccines have proven to be highly efficacious and effective in preventing HPV infection, genital warts, precancerous lesions, and cervical cancer. Recent studies also indicate that birth outcomes might be positively affected by HPV vaccination. However, long-term safety data regarding the impact of HPV vaccination on adverse pregnancy outcomes is absent. We aimed to evaluate the long-term association between the quadrivalent HPV vaccine and adverse pregnancy outcomes, leveraging nationwide high-quality Swedish register data

Methods: We included 470,000 singleton pregnancies (gestational week ≥22 weeks) among nulliparous women aged 16 to 35 in Sweden between Jan 1, 2006 and 31 Dec, 2018. We obtained the exposure to quadrivalent HPV vaccination, pregnancy outcomes and confounding variables from nationwide Swedish registers, linked at individual level. Confounding variables were: county of residence, calendar year of delivery (as a continuous variable), mother's country of birth, highest educational level, highest annual household income level, maternal age (as a spline term with 5 degrees of freedom), smoking, body mass index, assisted reproduction and maternal diagnoses . We estimated the risk of adverse pregnancy outcomes including stillbirth, preterm delivery, premature rupture of membranes (PROM) at 37+ weeks, preterm premature rupture of membranes (pPROM), low birth weight, small-for-gestational age, neonatal mortality and medically induced delivery in relation to HPV vaccination prior to child birth. We also performed a sensitivity analysis where women receiving quadrivalent HPV vaccination after the onset of pregnancy (n~100) were excluded.

Results: After controlling for potential confounders, we found a 13% lower risk (OR 0.87; 95% CI, 0.80 to 0.95) for small-for-gestational age among vaccinated women in comparison to not vaccinated women. In the main analysis we observed point estimates below unity for stillbirth, moderately preterm, PROM in deliveries at 37+ weeks and low birth weight, but none of these were statistically significant. No statistically significant differences were found for other pregnancy outcomes including preterm delivery, pPROM, neonatal mortality and medically induced delivery. In the sensitivity analysis the lower risk for SGA after quadrivalient HPV vaccination was confirmed, and there was also a statistically significant lower risk for stillbirth (OR 0.78; 95% CI, 0.61 to 0.99).

Conclusions: We found no evidence that quadrivalent HPV vaccination should be associated with elevated long-term risk of adverse pregnancy outcomes. We also found indications of lower risks for SGA and stillbirth, although possible mechanisms behind this could not be tested in the current study.

Acuti Martellucci Cecilia
Italy
Acuti Martellucci Cecilia
Italy

#3267

EFFECTIVENESS OF VACCINATION RE-INVITATION AT 25 YEARS OF AGE TO INCREASE HPV VACCINE UPTAKE

06 - HPV prophylactic vaccines

Acuti Martellucci C[1], Morettini M[2], Massetti L[2], Flacco M[1], Manzoli L[3], Giacomini G[2], Catalini A[4], Pasqualini F[2]

[1]Department of Medical Sciences, University of Ferrara, Ferrara, Italy

[2]Oncologic Screening Unit, Area 2 of the Marche Region Healthcare Agency, Ancona, Italy

[3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[4]Department of Biomedical Sciences and Public Health, University of the Marche Region, Ancona, Italy

Background/Objectives: The HPV vaccine was found to be highly effective against cervical cancer (Lei et al, NEJM 2020). However, coverage of this vaccination is often lower than the 90% target, and several strategies have been implemented to try to increase vaccine uptake (Bruni et al, Preventive Medicine 2021). This study aims to assess whether re-inviting women aged 25 years was effective in increasing HPV vaccine uptake.

Methods: The Province of Ancona, Italy actively offers free HPV vaccination from age 12 years, and started with the 1996 birth cohort in 2009 (males were invited starting in 2017). This cohort was also the first to remain eligible for the vaccine until age 25 years: in 2021, unvaccinated women were actively re-invited in the context of the cervical screening campaign. Women had to send an email requesting the vaccine, and dedicated sessions were organised for the three doses (0, 2, and 6 months schedule). Data were collected from the official registries of the Local Health Agency, and the main outcome was the increase in uptake of at least two vaccine doses following the re-invitation.

Results: Out of the whole cohort of 2074 women, 66.0% were vaccinated with at least two doses in their adolescence, while the remaining (n=705) did not adhere to the vaccination and were thus actively invited for catch-up in 2021. Those requesting an appointment were 125 (17.7% of those invited). Of these, 27 did not show up for their first dose, for a final uptake of 13.9% (n=98). Thus, the overall uptake in this cohort increased from 66.0% to 70.7%.

Conclusions: Re-inviting the women who were not vaccinated up to 25 years of age increased by 5% the overall vaccine uptake, but 86% of the unvaccinated women still did not adhere. If these data are confirmed, the cost effectiveness of repeating the vaccination campaign should be carefully evaluated, as the available resources could be devoted to ensure the maximum immunization coverages among adolescents.

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Di Lorenzo Antonio
Italy

Di Lorenzo Antonio
Italy

#3808

Surveillance of adverse events following HPV9 vaccine in a Region which implemented UMV: data from Puglia (Italy)

06 - HPV prophylactic vaccines

Berardi P[1], Di Lorenzo A[1]

[1]Dipartimento di Scienze Biomediche e Oncologia Umana, Università degli Studi di Bari "Aldo Moro", Bari, Italy

Background/Objectives: Human Papillomavirus (HPV) is responsible for epithelial lesions and cancers in both males and females. The latest licensed HPV vaccine is Gardasil-9, a 9-valent vaccine effective both against high-risk HPV types and those responsible for non-cancerous lesions. The Italian Vaccination Schedule for Life of National Vaccine Prevention Plan 2017-2019 recommends 2 or 3 doses of HPV vaccine, according to the vaccine and the patient's age; the plan's targets are both males and females aged 12 and older and women over 25 years of age not yet immunized. Vaccination is also offered actively and free-of-charge to high-risk groups, such as MSM or women with HPV-related lesions. The surveillance of the safety profile of recently introduced vaccines is a key strategy for the success of immunization campaigns; in Italy, surveillance of Adverse Events Following Immunization (AEFIs) is carried out by the Italian Drug Authority (AIFA) in collaboration with Regional Health Authorities. This report describes the adverse events following Gardasil-9 administration reported in Puglia, a region in the South of Italy, from January 2018 to November 2021.

Methods: This is a retrospective observational study. Data about Gardasil-9 AEFIs were collected from AIFA's database. The overall number of Gardasil-9® doses administered during the study period was extrapolated from the regional online immunization database (GIAVA). AEFIs were classified as serious or non-serious accordingly to World Health Organization (WHO) guidelines, and serious ones underwent causality assessment, as recommended by WHO, in order to determine their causal association with the vaccination.

Results: During the study period, 266,647 Gardasil-9 doses were administered in Puglia and 22 AEFIs were reported, with a reporting rate (RR) of 8.25/105 doses. 15 out of 22 AEFIs regarded subjects under 18 years of age, and the male/female ratio was 0.833 (10 males vs. 12 females). Neurological symptoms were the most reported (7/22, RR: 2.62/105 doses), followed by local events of pain, swelling or erythema (6/22, RR: 2.25/105 doses) and allergic reactions (6/22, RR: 2.25/105 doses). 5 AEFIs (22.7%, RR: 1.87/105 doses) were serious, and 2 of these led to hospitalization. One case of permanent impairment occurred. Following causality assessment, only 2 out of 5 serious AEFIs were deemed consistently associated with the vaccination. One of them consisted in a severe skin rash localized to the torso followed by glottis oedema on the next day. The second one consisted in fainting, occurred one hour after the vaccine's administration. The RR for vaccine-related AEFIs was therefore 0.750/105 doses. 15 out of 22 AEFIs (68.2%) healed completely, while for 3 of them (13.6%) only partial healing occurred. 2 out of 22 patients (9.10%) were still suffering from the AEFIs, while for 2 the outcome is still not known.

Conclusions: Our data are similar to pre-licensure evidence as far as the AEFIs' nature is concerned. The RR though is far lower than the ones described in clinical trials; this may be due to the different data collection method: our study used passive surveillance, while pre-marketing studies generally employ active call. While allowing a closer surveillance of rare AEFIs, in fact, passive surveillance on large populations determines an increased risk of under-reporting, especially for mild AEFIs. Gardasil-9's safety profile seems favourable, with a low rate of serious adverse events and an advantageous risk/benefits ratio.

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Doshi Mishelben
United States

Luxembourg Alain
United States

#3633

LONG-TERM IMMUNOGENICITY AND EFFECTIVENESS OF THE 9-VALENT HPV (9vHPV) VACCINE IN PREADOLESCENTS AND ADOLESCENTS AFTER 10 YEARS OF FOLLOW-UP

06 - HPV prophylactic vaccines

Olsson S[1], Luxembourg A[2]

[1]Karolinska Institute, Danderyd Hospital, Stockholm, Sweden

[2]Merck , Kenilworth, United states

Background/Objectives: The 9-valent human papillomavirus (9vHPV) vaccine was developed to protect against infection and disease related to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The pivotal 36-month Phase III immunogenicity study of 9vHPV vaccine in boys and girls aged 9-15 years was extended to assess long-term immunogenicity and effectiveness through 10 years after the last 9vHPV vaccine dose (NCT00943722).

Methods: Participants aged 9-15 years who received three 9vHPV vaccine doses in the base study (Day 1, Months 2 and 6) were enrolled in the study extension (N=1272 [males, n=301; females, n=971]). Serum was collected at Day 1 and Months 7, 12, 24, 36, 66, 90, and 126 to assess antibody responses (by competitive Luminex immunoassay [cLIA; primary immunoassay] and IgG Luminex immunoassay [IgG-LIA]). For effectiveness analysis, genital swabs were collected (to assess HPV DNA by polymerase chain reaction PCR) and external genital examinations (to detect external genital lesions) were conducted every 6 months starting when participants reached age 16 years. Cervical cytology tests were conducted annually for females ≥21 years of age; participants with cytological abnormalities were triaged to colposcopy based on a protocol-specified algorithm. External genital and cervical biopsies on abnormal lesions were performed. Tissue samples were adjudicated by a pathology panel. Primary analyses were conducted in per-protocol populations.

Results: Geometric mean antibody titers peaked around Month 7, decreased most sharply between Months 7 and 12, then decreased gradually thereafter through Month 126. Seropositivity rates remained ≥81% by cLIA and ≥95% by IgG-LIA at Month 126 for each of the 9vHPV vaccine types. After up to 11.0 years (median 10.0 years) follow-up post-Dose 3, there were no cases of HPV6/11/16/18/31/33/45/52/58-related intraepithelial neoplasia or genital warts among male participants. Among females, there were no cases of high-grade HPV6/11/16/18/31/33/45/52/58-related intraepithelial neoplasia or genital warts and one case of HPV-16-related cervical intraepithelial neoplasia grade 1. Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in males and females in the per-protocol population were low (54.6 and 52.4 per 10,000 person-years, respectively) and within ranges expected in vaccinated cohorts, based on results from previous efficacy trials of the quadrivalent and 9vHPV vaccines.

Conclusions: The 9vHPV vaccine demonstrated sustained immunogenicity and effectiveness through approximately 10 years post-9vHPV vaccination of boys and girls aged 9-15 years.

Wu Elise
United States

Wu Elise

#3288

NEXT ERA OF HPV MODELS: A CLOUD-BASED USER-FRIENDLY DYNATIC TRANSIMISSION MODEL

36 - Economics and modelling

Wu E[1], Varga S[1], Sharma A[1], Palmer C[1], Kothari S[1], Dasbach E[1]

[1]Merck , Kenilworth, United states

Background/Objectives: Human papillomavirus (HPV) infection is a well-known cause of cervical cancer in woman. In addition, HPV infection is associated with diseases in men and women including anal and head and neck cancers as well as genital warts. HPV vaccination has been available since 2006 and over time has expanded in the breadth of the disease and populations that it covers. Given this, payers and policy decision-makers are interested in better understanding of the projected public health impact and cost-effectiveness (CE) of different HPV vaccination strategies holistically and timely. PRIME model, a static policy analysis tool, represents one of the publicly available models that evaluates the benefit of HPV vaccination in women for cervical cancer. Given its limited scope, several dynamic transmission models (DTM) have been developed capture the full spectrum of HPV vaccine benefit. DTM is complex, requiring calibrations and is time-consuming. Therefore, developing an agile and flexible tool that can execute multiple scenarios in real-time and in a user-friendly fashion is needed. The objective of this exercise is to develop a cloud-based Mathematica execution framework that could run multiple complex computations in parallel and help describe and capture the full value of HPV vaccination for a broad set of stakeholders.

Methods: Three steps were taken to transform a sophisticated standalone model into an agile and user-friendly application. First, A cloud-based epidemiologic and economic tool for nonavalent HPV vaccination was developed which combines DTM of HPV infection in heterosexual men and women with economic modeling to measure the CE of various vaccination strategies. Second, the model is managed by a single secure health economic platform that provides stable execution environments for multiple modeling technologies. It is a Model Hub for model developers and consumers to collaborate around uploading inputs, managing, and accessing information of health economic models and the platform provides several capabilities around storage, advanced search, model execution, parallel processing capabilities and version control for scripted language models. Finally, a user-friendly application is developed which allow user to evaluate various HPV vaccine strategies or scenarios in real-time by updating key parameters.

Results: A cloud-based DTM application was launched in 5 pilot counties. Health economists, policy decision-makers and payers utilized the tools to evaluate HPV vaccine benefit in various scenarios and selected the optimal vaccine strategies. The application is evolving continually in both functionalities and covered countries.

Conclusions: A cloud-based agile DTM is beneficial for the HPV community to demonstrate broad value of HPV vaccines in a timely fashion in discussion with key decision maker. This tool would allow HPV researchers to evaluate the long-term benefit of HPV vaccines in various scenarios to determine the optimal vaccination programs.

Bonawitz Rachel
United States

Bonawitz Rachel
United States

#3999

IMMUNOGENICITY OF 2-DOSE REGIMENS OF 9 VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE WITH EXTENDED DOSING INTERVALS: INTERIM RESULTS OF PROTOCOL V503-069

06 - HPV prophylactic vaccines

Bonawitz R[1]

[1]Merck , Kenilworth, United states

Background/Objectives: HPV vaccines are licensed as 2-dose regimen (administered 6 to 12 months apart) in 9-14-year-olds. Immunogenicity of dosing intervals >12 months is not well-characterized. Protocol V503-069 [NCT04708041] is an international, open-label study to evaluate the safety and immunogenicity of extended dosing intervals described previously (1). This interim analysis characterizes the immunogenicity and safety of the 9vHPV vaccine in boys and girls 10-15 years of age who received one dose of commercial 9vHPV vaccine dose (Dose 1) at least 1 year prior to study start and received a second dose (Dose 2) on Day 1 of the study.

Methods: Serum anti-HPV6/11/16/18/31/33/45/52/58 antibodies were evaluated by competitive Luminex Immunoassay at Day 1 and 4 weeks postdose 2. Anti-HPV GMTs at 4 weeks postdose 2 were evaluated with simple linear regression modeling, accounting for time interval between administration of Dose 1 and Dose 2. The impact of time interval between doses on the expected GMT was estimated as a change (increase or decrease) in the unadjusted GMT for every unit increase in time between doses. Participants were followed for injection-site and systemic adverse events (AEs) 15 days after each vaccination, and serious AEs for duration of participation.

Results: 146 participants enrolled and received 9vHPV vaccine on Day 1. The majority (96.6%) completed the trial 4 weeks postdose 2. Time between doses varied (median = 2.1 years; range 1.0 to 4.4 years). The geometric mean titers (GMTs) in mMU/mL at Day 1 represent GMTs corresponding to varying lengths of time postdose 1, ranging from 16.3 (HPV 45) to 104.6 (HPV 16). The GMTs at Month 1 represent GMTs at 4 weeks postdose 2 and ranged from 507.1 (HPV 45) to 22,237.2 (HPV 16). The data support a fold-change of 1.0 in unadjusted GMTs (i.e., unadjusted GMT x 1.0) for every 6 months increase in time interval between doses. No serious AEs were observed among participants.

Conclusions: This interim analysis is the first to describe immunogenicity and safety of extended interval dosing regimens of 9vHPV vaccine in adolescents. With a minimum interval of 1 year between the 2 doses of 9vHPV vaccine, the GMT at 4 weeks following the second dose of 9vHPV vaccine was not impacted by the varying time interval between doses (1 year to 4.4 years). The study is ongoing with additional analyses in cohorts of 9-14 year-old boys and girls who receive 2 doses at various intervals to demonstrate non-inferior immunogenicity of extended intervals compared with 16-26 year-old women who receive 3 doses.

References: 1. Teppler H et al. Design of a Phase III immunogenicity and safety study evaluating two-dose regimens of 9-valent human papillomavirus (9vHPV) vaccine with extended dosing intervals. Contemp Clin Trials: 2021 Jun;105:106403.

Doshi Mishelben
United States

Lily Wu
China

#3580

IMMUNOGENICITY AND SAFETY STUDY OF THE 9vHPV VACCINE IN 9-45-YEAR-OLD CHINESE FEMALES

06 - HPV prophylactic vaccines

Liao X[1], Chen Z[2], Lv H[2], Wang S[2], Liang Z[2], Yan C[3], Yu W[4], Fu R[1], Shou Q[1], Chen Y[1], Song Y[1], Zheng M[1], Luxembourg A[5], Lily W[1]

[1]MSD R, Beijing, China

[2]Zhejiang Provincial Center for Disease Control and Prevention, Zhejiang, China

[3]Kaihua County Center for Disease Control and Prevention, Zhejiang, China

[4]Keqiao District Center for Disease Control and Prevention, Zhejiang, China

[5]Merck , Kenilworth, United states

Background/Objectives: The 9-valent human papillomavirus (9vHPV; HPV6/11/16/18/31/33/45/52/58) vaccine was conditionally approved for Chinese women (16-26 years) in 2018 based on global data. This is one of two post-marketing committment studies of 9vHPV vaccine in Chinese females. Dual-primary objectives of this study (NCT03903562) were to demonstrate non-inferiority of anti-HPV geometric mean titers (GMTs, 9-19 vs 20-26 years) and seroconversion (27-45 vs 20-26 years).

Methods: Participants (N=1990; 9-19 years: n=690; 20-26 years: n=650; 27-45 years: n=650) were enrolled to receive three doses of 9vHPV vaccine (Months 0, 2, 6). Serum samples were collected (Day 1, 1 month post-Dose 3) and tested by competitive Luminex immunoassay. For each HPV type, non-inferiority criterion for GMT required the lower bound of the two-sided 97.5% confidence interval (CI) of GMT ratio (9-19 vs 20-26-year olds) to be >0.67, and for seroconversion, the lower bound of the two-sided 97.5% CI in differences (27-45 minus 20-26-year olds) was to be >-5%. Immunogenicity analyses were based on the per-protocol population. Adverse events (AEs) were recorded.

Results: Robust anti-HPV GMTs were observed at 1 month post-Dose 3 in study participants. Nearly all (≥99.8%) participants seroconverted to all vaccine HPV types. Prespecified statistical criteria for GMTs/seroconversion rates were met for all vaccine HPV types, demonstrating that antibody responses in 9-19-year olds and 27-45-year olds were non-inferior to those in 20-26-year olds (all P values <0.0001). Injection-site AEs and systemic AEs were reported by 43.3% and 50.9% of 9-19-year olds, 50.5% and 57.1% of 20-26-year olds, 43.8% and 43.4% of 27-45-year olds, respectively. No vaccine-related serious AEs and no deaths were reported.

Conclusions: 9vHPV vaccine-induced antibody responses were non-inferior in Chinese females 9-19 and 27-45 years of age versus 20-26 years of age. The vaccine was generally well tolerated in these populations.

Doshi Mishelben
United States

Luxembourg Alain
United States

#3584

IMMUNOGENICITY OF 1, 2, AND 3 DOSES OF 9-VALENT HUMAN PAPILLOMAVIRUS (9vHPV) VACCINE IN GIRLS 9-14 YEARS OF AGE

06 - HPV prophylactic vaccines

Luxembourg A[1], Bautista O[1], Saah A[1]

[1]Merck , Kenilworth, United states

Background/Objectives: In an open-label, randomized clinical trial, 2 doses of 9vHPV vaccine, given 6 or 12 months apart, induced non-inferior antibody responses in 9- to 14-year-olds compared with young women 16-26 years who received 3 doses (i.e., the age group and dose regimen in which vaccine efficacy was established). Thus, efficacy of 2 doses of the 9vHPV vaccine in 9- to 14-year-olds was inferred, which supported licensure of a 2-dose regimen in this population. We report results of exploratory immunogenicity analyses of this trial from girls 9-14 years who received 1, 2, or 3 vaccine doses.

Methods: Girls 9-14 years (N=753) were randomized in a 2:1:2 ratio to 0,6 cohort (2 doses given at 0 and 6 months), 0,12 cohort (2 doses given at 0 and 12 months), and 0,2,6 cohort (3 doses given at 0, 2, and 6 months). Young women 16-26 years (N=314) were enrolled to receive 3 doses. Blood was collected before dose 2 at Months 1 (0,6 cohort subset: n=50) and 6 (0,6 cohort), and Month 12 (0,12 cohort), and after the final dose at Months 7, 12, 24, and 36 (0,6 and 0,2,6 cohorts) or Months 13, 24, and 36 (0,12 cohort). HPV antibody responses to the 9 vaccine HPV types were assessed by competitive Luminex immunoassay (cLIA).

Results: Most (>99%) girls receiving 2 or 3 doses seroconverted for the 9 HPV vaccine types at 1 month post last dose. Anti-HPV geometric mean titers (GMTs) were highest at 1 month post last dose, decreased sharply during the subsequent 12 months, and then decreased more slowly. GMTs at 1 month post last dose in girls receiving 2 or 3 doses were similar to or greater than GMTs in young women receiving 3 doses. This trend was still observed through 24-30 months post last dose. A single dose of vaccine resulted in partial seroconversion (41% to 98% at 6 months after a single dose, depending on the HPV type, vs 97% to 100% at 6 months after completion of the 0,6 regimen) and lower GMTs than after 2 or 3 doses (6- to 14-fold lower than after the 0,6 regimen at 6 months post last dose). Percent seropositivity and GMTs after a single dose declined over time during the observation period (i.e., through 12 months post dose).

Conclusions: Immunogenicity assessment of 2- and 3-dose schedules of the 9vHPV vaccine suggests that 2 properly spaced doses elicit protective antibody response and durable protection. Antibody responses after a single dose were less robust than after 2 or 3 doses. It is unknown whether a 1-dose schedule elicits long-term protective antibody responses.

FC 04 - Viral and molecular biology

Wei Ye Ye Wei
China

#3372

Single-cell Profiling Analysis Reveals that Targeting CXCR4+ CD8 T cells Promotes anti-PD-1 Immunotherapy of Cervical Cancer

26 - Cervical neoplasia

Canhui C[1], Ye W[1], Shitong L[1], Wenhua Z[1], Ting P[1], Chao H[1], Tian C[1], Binghan L[1], Wencheng D[1], Ding M[1], Peng W[1]

[1]Department of Gynecologic Oncology, Tongji Hospital , HUST, Wuhan, China

Background/Objectives: Since anti-programmed cell death 1 (PD-1) immunotherapy has limited effect in cervical cancer, alternative co-target pathways in the tumor immune microenvironment (TIME) are underscoring. CXC chemokine receptor 4 (CXCR4) blockade facilitated immunotherapy in many cancer types. However, the mechanisms of targeting CXCR4 underlying tumor infiltration remain to be determined.

Methods: Single-cell transcriptome data of skin, liver, lung, prostate, colon, cervix, uterus, cervical cancer, endothelial cells, stem cells, pancreatic progenitor cells, nasal airway epithelium, breast epithelium, peripheral blood mononuclear cells (PBMCs), T cells, B cells, CD34+ cells, and CD14+ cells were analyzed to identify the specific expression of CXCR4 in CD8 T cells. In addition, RNA-seq data from the TCGA were integrated to demonstrate the correlation of CXCR4+ CD8 T cells in suppressive TIME of cervical cancer. Furthermore, CXCR4 inhibitors and agonists were used to explore the effects of targeting CXCR4+ CD8 T cells in promoting anti-PD-1 immunotherapy.

Results: Single-cell transcriptome analysis of multi-tissues and multi-cells revealed that CXCR4 was specifically expressed in T cells. Further analysis of single-cell profiling of the cervix and uterus demonstrated that CXCR4 was specifically expressed in CD8 T cells, with a positive correlation with the expression of PD-1 in cervical cancer. In TIME of cervical cancer, CXCR4+ CD8 T cells were associated with lymphocyte activation and tumor immune cell infiltration. By inhibiting the expression of CXCR4 via BL-8040 and AMD3100, the expression of PD-1 was reduced in concentration dependence, with the the upregulation of PI3K-AKT-mTOR pathway. In addition, the expression patterns were reversed via the CXCR4 agonist, NUCC-390. Moreover, in vivo assays found that inhibiting CXCR4 promotes anti-PD-1 immunotherapy of cervical cancer via remodeling TIME.

Conclusions: Overall, single-cell profiling analysis reveals that CXCR4 was specifically expressed in CD8 T cells in cervical cancer, and combined CXC4 and PD-1 blocked may expand the benefit of immunotherapy in cervical cancer.

Renner Janis
Germany

Renner Janis
Germany

#3394

BRD4S INTERACTS WITH VIRAL E2 PROTEIN TO LIMIT HUMAN PAPILLOMAVIRUS LATE TRANSCRIPTION

02 - Viral and molecular biology

[1]Institut für Medizinische Virologie und Epidemiologie der Viruskrankheiten, Tübingen, Germany

Background/Objectives: Papillomaviruses have coevolved with their host by using cellular factors like Bromodomain containing protein 4 (Brd4) to support genome maintenance, gene transcription and replication. The C-terminal domain (CTD) of Brd4 represents a highly conserved binding site for the N-terminal domain of E2, which is important for its transcription activator function. Recently the PDID (phosphorylation dependent interaction domain) of Brd4 was described as an additional interaction site for E2. In addition to full-length Brd4 a short isoform of Brd4 (Brd4S) is expressed which contains the PDID but lacks the CTD and thus might interact with E2. Therefore, we analyzed the interaction of Brd4S and E2 and explored its functional consequences.

Methods: We used flow cytometry based-FRET analysis and co-immunoprecipitations to analyze protein-protein interactions, chromatin-immunoprecipitation (ChIP) to study interaction with the viral origin, immunofluorescence analysis for co-localization studies. SiRNA knockdown were used to determine viral transcription and replication activities in undifferentiated and differentiated cells

Results: We confirmed that the isolated CTD and PDID of Brd4 interact with E2 by FRET assays. Consistent with this, Brd4S co-immunoprecipitated with HPV31 E2. Immunoblot analyses indicated that Brd4S is present in significant amounts in HPV-negative and -positive keratinocytes. Immunofluorescence analysis revealed a partial co-localization of Brd4S with E2 in the nucleus which was greatly enhanced by the presence of the E1 protein and the viral origin. Consistent with this, ChIP-experiments revealed that BRD4S binds to the viral origin. Knockdown and overexpression studies indicated that Brd4S inhibits E2´s transactivation function. In line with this, knockdown of BRD4S induced viral late transcription in undifferentiated cells maintaining replicating HPV31 genomes.

Conclusions: Our study reveals an inhibitory role of BRD4S on HPV transcription, which may serve as an immune escape mechanism by the suppression of L1 transcripts and thus contribute to the establishment of persistent HPV infections.

Guimarães Yasmin
Brazil

Yasmin Guimarães
Brazil

#3758

Characteristics of ancestry patterns of multiracial women population with cervical lesions induced by HPV: Preliminary results from H2020 Elevate Study.

02 - Viral and molecular biology

Yasmin G[1], Luani G[1], Tauana D[1], Nathalia C[1], Heleen V[4], Olivier D[4], Ricardo D[2], Adhemar L[1,3]

[1]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil

[2]Department of Gynecologic Oncology, Barretos Cancer Hospital, Barretos, Brazil

[3]School of Medicine, University of Minho, Braga, Portugal

[4]Department of Public Health , Gent, Belgium

Background/Objectives: Cervical cancer remains a public health problem worldwide, especially in middle and low-income countries as Brazil. The responsible for this tumor is the human papillomavirus (HPV), most notably types 16, 18 and 12 other high-risk types, capable of infecting epithelial tissues of the human body, especially the cervix. This infection is considered the most common sexually transmitted disease in the world and, in most cases, is eliminated by the immune system without major complications. However, persistent infection can induce carcinogenesis. Currently, the meaning of the infected woman's ancestry in the persistence of the HPV infection and the risk of developing cancer has been documented. However, in Brazil that has a highly admixed population, the knowledge about the biological influence of ancestry in cervical cancer is still incipient; for this reason, it is important to investigate whether differences in persistence caused by the women's ancestry can influence the HPV infection profile in distinct populations. Thus, we aimed to characterize the genetic ancestry of 500 Brazilian (250) and Belgium (250) women and to associate it with age, cytology status, and HPV genotyping data.

Methods: Liquid-based cervical samples are being used for ancestry and HPV genotyping. Ancestry analysis is performed using a set of 46 ancestry-informative markers (AIMs) among the most informative insertion and deletion polymorphisms (INDELs) for each population group. A 46plex PCR is performed and the amplified products are subsequently submitted to capillary electrophoresis in the ABI 3500 xL sequencer (Applied Biosystems). The electropherograms are analyzed and the genotypes are automatically assigned with GeneMapper v4.1 (Applied Biosystems). The proportions of ancestry are assessed using the Structure v2.3.3 software, considering the four main parental population groups: Native Americans, Europeans, Africans, and Asians as possible contributors to the current genetic background of the general population. For HPV genotyping, Cobas® 4800 HPV Test (Roche) is used. This PCR automatized platform can identify the infections by HPV16, HP18 and/or a pool of other 12 high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 59, 66, 68). Statistical analysis will be performed with the Software SPSS 25.0 (IBM Corp) and only results with a p-value <0.05 will be considered significant.

Results: So far, 239 cases were fully analyzed for genetic ancestry. The estimated proportion of ancestry for Brazilian women is European=67%, African=15%, Native American=12%, and Asian=6%. For Belgium women, the estimation is European=89%, African=5%, Native American=3% and Asian=3%. Regarding HPV genotyping, 374 samples were already tested. For the 194 Brazilian samples, 57.3% were negative; among the positive ones, 28.6% were positive for the other 12 high-risk HPV types, 6.8% were positive for HPV16, 1.6% HPV18, 3.6% coinfection of others and 16, 1% coinfection of others and 18, 0.5% coinfection of 16 and 18, and 0.5% coinfection of other, 16 and 18. For the 180 Belgium samples, 68.8% were negative; among the positive ones, 18.8% were positive for the other 12 high-risk HPV types, 3.1% positive for HPV16, 1% for HPV18, and 1.6% coinfection of others and 16.

Conclusions: In the near future, we expect to verify if the HPV infection profile of Brazilian and Belgium women is associated with significant lesions' behavior differences when clustered by genetic ancestry, age, and cytology status.

Li Boning
China

Li Boning
China

#3619

25-hydroxycholesterol inhibits human papllomavirus infection in cervical epithelial cells via disturbance of cytoskeleton remodeling through lipid metabolism suppression

02 - Viral and molecular biology

Li B[1], Hua C[2], Lu L[2], Sui L[1]

[1]Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China

[2]Key Laboratory of Medical Molecular Virology (MOE/NHC/CAMS), School of Basic Medical Sciences, Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai, China

Background/Objectives: In spite of the fact that several prophylactic vaccines have been approved for prevention of high-risk human papillomavirus (HPV) infection and the occurrence of cervical cancer, not all high-risk HPV types are included in the vaccines; therefore broad-spectrum therapeutic strategies for HPV infection are crucial. 25-hydroxycholesterol (25HC) is the enzymatic product of cholesterol 25-hydroxylase (CH25H), which is encoded by an interferon-stimulated gene (ISG). It has recently been identified as a cholesterol biosynthesis regulator and virus repressor, targeting entry of enveloped virus, including SARS-CoV-2. However, the mechanisms of 25HC to limit non-enveloped viruses, such as HPV, remain to be explored. Here we investigated the anti-HPV potency of 25HC and illustrated probable mechanisms of this virus infectivity inhibitor.

Methods: We used HPV pseudoviruses (PsV) with reporter genes to identify the capability of 25HC to protect cervical epithelial cells from multi-types of HPV infection. IVIS in vivo imaging system was applied to evaluate the potency of 25HC in HPV infection prevention in a murine model. Immunofluorescence assays were conducted to determine the involvement of actin filaments in 25HC antiviral effect. RNA-seq, Western blot and Rho pull-down assays were used to study cytoskeleton reorganization mechanisms after 25HC treatment.

Results: 25HC exhibited broad-spectrum anti-HPV activity in cervical epithelial cells. Intravaginally applied and intraperitoneally applied 25HC inhibited HPV infection and reduced viral load in the cervical region of murine genital challenge models. 25HC did not block HPV PsV interaction with cervical epithelial cell receptors, but rather regulated cellular milieu. During HPV infection, 25HC disturbed cytoskeletal remodeling in cervical epithelial cells, which is reported to be vital in virion transportation. Further analysis revealed that, 25HC inhibited isoprenoid biosynthetic process and subsequently restricted prenylation of Rho GTPases. The decreased prenylation suppressed Rho GTPases activation, then restrained LIMK/cofilin activation, and ultimately interfered with polymerization status of filopodia and stress fibers.

Conclusions: Here we show a previously unrecognized role of 25HC in influencing cytoskeleton remodeling through its cholesterol regulator capacity. Dysfunction of actin filaments dynamics plays a critical role in the suppression mechanism of 25HC against HPV infection. Our study provided new clues and theoretical basis for therapeutic targets of HPV infection.

Kldiashvili Ekaterina
Georgia

Iordanishvili Saba
Georgia

#3547

rs2232365 Polymorphism of FOXP3 Gene as a Risk Factor of Cervical Cancer Development

02 - Viral and molecular biology

Kldiashvili E[1], Metreveli T[1], Iordanishvili S[1], Al-rustum S[1]

[1]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia

Background/Objectives: Cervical cancer is the second common malignancy in women. This is an immunogenic malignancy, and high-risk human papilloma virus (HPV) subtypes may cause its development. Persistent infection of high-risk HPV subtypes may significantly facilitate the development of cervical intraepithelial neoplasia, which has been confirmed as a major risk factor of cervical cancer. Regulatory T cells (Treg cells) are a group of mature T cells generated in the thymus following the induction of peripheral naïve T cells. They are essential for the inhibition of immune overreaction induced damage, but over-production of Treg cells may block the protective immune response to infection and tumors. FOXP3 (Forkhead box protein P3) is a key transcription factor in regulatory T cells (Tregs), and has important roles in the immunosuppressive functions in Tregs. The role of FOXP3 gene polymorphisms in cancer patients is not determined till now.

Methods: The allele-specific polymerase chain reaction (AS-PCR) has been used for determination of FOXP3 gene rs2232365A/G polymorphism in collected plasma samples. A total 100 plasma samples have been collected from the patients of the Research Institute of Clinical Medicine (Tbilisi, Georgia) in May-August 2019. 90 samples have been collected from the patients with diagnosed cervical cancer (34 plasma samples) and cervical intraepithelial neoplasia (CIN, 56 plasma samples). 10 plasma samples have been collected from the patients negative for intraepithelial lesion or malignancy; these samples have been used as a control group. The communication with patients, collection and labelling of the plasma samples has been performed by the responsible medical staff of the Research Institute of Clinical Medicine. The plasma samples have been provided to the research group anonymously; determination of sample category (i.e., patient with diagnosed cervical cancer / patient with diagnosed CIN /control group) by labeling was impossible.

Results: The present study aimed determination of FOXP3 gene rs2232365A/G polymorphism in collected plasma samples of patients with diagnosed cervical cancer and CIN in comparison with control group. rs2232365A/G polymorphism has been detected in 75.33% of cervical cancer (25 cases, $p = 0.03$) and 64.29% of CIN (36 cases, $p = 0.02$). FOXP3 gene rs2232365A/G polymorphism has not been detected in control group ($p = 0.01$). Treg cells have the key role in the process of immune escape. Their development requires continued expression of Foxp3; attenuated Foxp3 expression results in its functional deficiency. By analysis of the obtained results, we assume that polymorphisms of the Foxp3 gene may contribute to the cervical cancer development.

Conclusions: The present study revealed the link of rs2232365A/G polymorphism of FOXP3 gene with cervical cancer development.

Dong Zhe
China

Dong Zhe
China

#3685

New evidence of methylation biomarkers in cervical adenocarcinoma especially HPV independent type

15 - Molecular markers

Dong Z[1], Ren Z[1], Liu C[1], Xia W[1], Li T[2], Xiong G[1]

[1]Department of Gynecology and Obstetrics, Peking University International Hospital, Beijing, China

[2]Department of Pathology, Peking University International Hospital, Beijing, China

Background/Objectives: Although cervical cancer screening and the use of HPV vaccine have greatly decreased the incidence of cervical cancer, the frequency of cervical adenocarcinoma (CAC) has increased these years. About 2/3 (60.3%) of CAC patients are younger than 50 years old. The three-step cervical cancer screening process is not suitable for early detection of CAC because the lesion is located in the cervical canal or HPV independent type. The main purpose of this study is to find clinical evidence of CisCer DNA-methylation test (methylated PAX1 and JAM3 gene) in CAC, especially HPV independent type.

Methods: 10 paraffin block carcinoma tissues and 17 liquid-based cytology (LBC) specimens of CAC were collected from Peking University International Hospital. The results of LBC, HPV genotyping test, immunohistochemical staining (p16 &ki67), and methylation test were compared and analyzed. Paraffin blocks and cervical exfoliated samples were subjected to DNA extraction, bisulfite conversion and DNA methylation detection in CisCer DNA methylation detection system according to the manufacturer's protocol (CISPOLY Co., Beijing, China).

Results: The 10 tissue samples of CAC included 4 common types, 3 neuroendocrine types and 3 gastric types. The positive rate of tests was high-risk HPV (hrHPV; 70.0%), HPV16/18 (60.0%), LBC (^{3}ASCUS; 70.0%), LBC (^{3}LSIL; 50.0%), p16 (partially +; 60.0%), ki67 (80.0%), and CisCer methylation (90.0%), respectively. The 17 cervical exfoliated cells of CAC were collected for cytology, HPV genotype, and methylation detection. The positive rates of tests were hrHPV (76.5%), HPV16/18 (58.8%), LBC (^{3}LSIL; 41.2%), LBC (^{3}ASCUS; 82.4%), and CisCer methylation (88.2%). In addition, the positive rate of CisCer methylation in rare cervical cancer was 100.0%, including gastric type (HPV independent) and neuroendocrine type, which were better than hrHPV and LBC testing.

Conclusions: In this study, new evidence from paraffin blocks and cervical exfoliated cell samples showed that the coincidence rate between CisCer methylation test and cervical adenocarcinoma was higher than that of other tests, especially HPV independent (gastric type). Methylation test can be used as a noninvasive detection of cervical adenocarcinoma including HPV independent and non-independent types in the future, which needs more evidence.

Reddin Ian
United Kingdom

Reddin Ian
United Kingdom

#3565

INTEGRATED ANALYSIS OF CERVICAL SQUAMOUS CELL CARCINOMA COHORTS FROM THREE CONTINENTS REVEALS CONSERVED SUBTYPES OF PROGNOSTIC SIGNIFICANCE

02 - Viral and molecular biology

Chakravarthy A[1], Reddin I[2], Henderson S[3], Dong C[4], Kirkwood N[4], Jeyakumar M[4], Rothschild Rodriguez D[4], Gonzalez Martinez N[4], Mcdermott J[5], Su X[6], Egawa N[7], Fjeldbo C[8], Skingen V[8], Halle M[10], Krakstad C[10], Soleiman A[11], Sprung S[12], Ellis P[4], Wass M[4], Michaelis M[4], Lyng H[8,9], Fiegl H[13], Salvesen H[10], Thomas G[2], Doorbar J[7], Chester K[5], Feber A[14,15], Fenton T[2,4]

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
[2]Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, United kingdom
[3]UCL Cancer Institute, Bill Lyons Informatics Centre, University College London, London, United kingdom
[4]School of Biosciences, Division of Natural Sciences, University of Kent, Canterbury, United kingdom
[5]UCL Cancer Institute, University College London, London, United kingdom
[6]MD Anderson Cancer Center, Houston, United states
[7]Department of Pathology, University of Cambridge, Cambridge, United kingdom
[8]Department of Radiation Biology, Oslo University Hospital, Oslo, Norway
[9]Department of Physics, University of Oslo, Oslo, Norway
[10]Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen, Norway
[11]INNPATH, Institute of Pathology, Tirol Kliniken Innsbruck, Innsbruck, Austria
[12]Institute of Pathology, Medical University of Innsbruck, Innsbruck, Austria
[13]Department of Obstetrics and Gynaecology, Medical University of Innsbruck, Innsbruck, Austria
[14]Centre for Molecular Pathology, Royal Marsden Hospital Trust, London, United kingdom
[15]Division of Surgery and Interventional Science, University College London, London, United kingdom

Background/Objectives: Human papillomavirus (HPV)-associated cervical cancer represents one of the leading causes of cancer death worldwide1. Although low-middle income countries are disproportionately affected, our knowledge of the disease predominantly originates from populations in high-income countries. The relationship, if any, between HPV type and cervical cancer prognosis remains unclear2. Using data from 643 cervical squamous cell carcinoma (CSCC) tumours from USA, Europe and Sub-Saharan Africa, we set out to test the hypothesis that we could identify a set of transcriptional and epigenetic features associated with prognosis within CSCC and to establish whether it is also present in independent patient cohorts representing different geographical locations.

Methods: Unsupervised clustering of a discovery cohort from the USA (n=236) using transcriptional data was performed to identify possible subtypes of CSCC. A methylation signature derived from resulting subgroups was used to develop a support vector machine (SVM) classification model that allocated European (n=313) and Sub-Saharan (n=94) validation cohorts to a particular subtype. Prognostic differences between subgroups were calculated using Cox regression multivariate analysis controlling for stage, age, HPV type and treatment.

Results: We identified two CSCC subtypes (C1 and C2) with differing prognosis, independent of HPV type. The poor prognosis associated with C2 tumours in the discovery cohort from the USA was also seen in the European validation cohort. The hazard ratio for C2 tumour 5-year survival obtained from multivariate analysis was 2.56 ($p = 0.002$), consistent with that seen in the discovery cohort ($HR = 2.44$, $p = 0.02$). C1 tumours were largely HPV16-driven, displayed increased cytotoxic T-lymphocyte infiltration and frequently harboured PIK3CA and EP300 mutations. C2 tumours were frequently driven by HPVs from the HPV18-containing alpha-7 clade, harboured alterations in the Hippo signalling pathway and increased expression of immune checkpoint genes, B7-H3 (also known as CD276), NT5E (also known as CD73) and PD-L2 (also known as PDCD1LG2).

Conclusions: In conclusion, we identify two novel, therapy-relevant CSCC subtypes. The key characteristics of these subtypes are conserved across the three cohorts, from the USA, Europe and Sub-Saharan Africa, thus our findings are likely of broad significance.

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Moreno Acosta Pablo
Colombia

Moreno-acosta Pablo
Colombia

#3757

Predictive factors of response to treatment in invasive squamous cell cancer of the cervix

15 - Molecular markers

Moreno-acosta P[1], Gonzalez-prieto C[2], Gamboa O[1], Malaver G[1], Magné N[3]

[1]National Cancer Institute, Bogota, Colombia

[2]Universidad Nacional de Colombia, Bogota, Colombia

[3]Clinique Pasteur, Tolouse, France

Background/Objectives: The most important risk factor for cervical cancer is HPV. Patients with cervical cancer in stages IIB and IIIB treated at the National Cancer Institute (Colombia) present a poor response to treatments such as radiotherapy (RT), at least 40% of these do not respond adequately. Within tumoral microenvironment, hypoxia in solid tumors, such as cervical cancer, induces genomic and proteomic changes, such as, for example, in IGFIR, GLUT1, HIF1a and hTERT, E6 HPV, changes that modulate response to treatment. We evaluate the possible relationship of the expression of the proteins IGF1Rß, hTERT, HIF1a, GLUT1, the presence of certain HPV16 species and some clinical parameters with the response to radiochemotherapy and radiotherapy.

Methods: Type-specific HPV infection was detected using GP5 + / GP6 + PCR-RLB, and expression of the IGF1R, hTERT, HIF1a, GLUT1 proteins by immunohistochemistry in 21 patients with invasive squamous cell carcinoma of the cervix.

Results: HPV16 was the most frequent type followed by HPV58 and HPV56. HPV16 alpha 9 species was the most frequent, followed by alpha 6 and alpha 7. IGF1R was expressed in 85.7%, HIF1a in 61.9%, GLUT1 in 52.3% and hTERT was detected in both the cytoplasm and the nucleus. with the same frequency (90.4%). Hgb levels ≤ 11d / dL (anemic hypoxia) were found in 28.6% and Hgb> 11 g / dL in 71.4%. 57.1% of the patients received radio chemotherapy and 42.9% exclusive radiotherapy. From the descriptive analysis of multiple correspondence in which two factorial axes were used accumulating 45.97% of the total variance, the MCA factor map showed a relationship between: nuclear and cytoplasmic expression of hTERT, and alpha 7 and alpha 9 species HPV16, observing similarity between HPV16 alpha 6 species and no expression of hTERT; GLUT1 and HIF1a; Hgb levels ≤ 11d / dL and no response to radiotherapy, such as between Hgb levels ≤ 11d / dL, expression of GLUT1 and HIF1a; HIF1a expression and hTERT expression; complete response and having received radio chemotherapy. In addition, a close relationship was observed between the nuclear and cytoplasmic expression of hTERT and the expression of IGFR1ß, a relationship that was confirmed by applying Fisher's exact test (p = 0.041).

Conclusions: A better response to radiochemotherapy than to radiotherapy was confirmed, as well as non-response in the presence of anemic hypoxia and HIF1a expression. One of the findings was the subcellular location of hTERT, the possible relationship between alpha 7 and alpha 9 species of HPV16 and the expression of the hTERT protein, in addition, the relationship between the expression of hTERT and IGF1R, interaction that could contribute to resistance to radiation therapy.

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FC02 - Screening methods and triage 2

Ring Linea Landgrebe
Denmark

Ring Linea L.
Denmark

#3500

PARTICIPATION IN CERVICAL CANCER SCREENING AMONG OVERWEIGHT AND OBESE WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

11 - Screening for women difficult to reach

[1]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
[2]Department of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Background/Objectives: The incidence of cervical cancer has decreased after implementation of cervical cancer screening. However, obese women have higher risk of cervical cancer than women of normal weight. Previous studies have found lower rates of participation in cervical cancer screening among obese compared to non-obese women, but an overview of the literature is lacking. We conducted a systematic review and meta-analysis of studies examining participation in cervical cancer screening among overweight and obese women compared to women with normal body mass index (BMI).

Methods: We conducted this systematic review and meta-analysis in accordance with PRISMA guidelines. The databases PubMed, Embase and the Cochrane Library were searched from 1 January 2000 to 12 July 2021 to identify English language studies reporting participation in cervical cancer screening among overweight or obese women compared to women with normal BMI. We included studies of women from the general female population eligible for cervical cancer screening. Data were extracted on the following variables: author, publication year, country, study design, study population, exclusion criteria, number of included women, age, race, screening interval, method of measuring screening participation and BMI, BMI categories, response rate to survey, statistical method, total number of women and number of women participating in screening in each BMI category, and relative risk estimates. Two reviewers independently extracted data, and inconsistencies were discussed to reach consensus. Furthermore, the quality of studies was scored using an adapted version of the New Castle-Ottawa scale. We plan to use a random effects model to estimate pooled odds ratios of screening participation comparing different BMI categories, e.g. overweight (BMI=25–30), obese class I (BMI=30–35) and obese class II (BMI=35–40), with women with normal BMI (BMI=18.5–25). Where possible, we will pool adjusted and unadjusted relative risk estimates separately.

Results: Our search identified 1676 records, of which we removed 247 duplicates. Titles (N=1429), abstracts (N=287), and full text articles (N=100) were reviewed by two authors independently. Reference lists were reviewed to identify additional relevant studies (N=9). Altogether, we included 57 studies.Data extraction for the study is ongoing. Results on relative risk of cervical cancer screening participation according to BMI will be presented at the conference.

Conclusions: To our knowledge, this is the first systematic review and meta-analysis of cervical cancer screening participation in overweight and obese women including data from a range of different countries.

Castañeda Kelly
Netherlands

Castañeda Kelly
Netherlands

#3713

HAS PARTICIPATION IN DUTCH CERVICAL CANCER SCREENING DECREASED IN THE LAST YEARS?

11 - Screening for women difficult to reach

Castañeda K[1], De Waard J[1], Vermeulen K[1], Greuter M[1], Van Der Vegt B[1], Siebers A[2], Sidorenkov G[1], Wisman B[1], Schuuring E[1], De Bock G[1]

[1]University Medical Center Groningen (UMCG), Groningen , Netherlands

[2]Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA), Houten, Netherlands

Background/Objectives: The benefits of regular cervical cancer screening (CCS) attendance are recognized worldwide (1). In The Netherlands, women aged 30-60 are invited to participate in the national CCS program every five years (2). In 2017, the screening changed from a cytology-based to an hrHPV-based program (3). Since then, the participation has decreased from 64% to below 57% (4). The participation rate is yearly provided by the CCS monitoring and is estimated within a 15-months window (4). As participation after that time window is not included in the estimates, this project aimed to evaluate the participation rate after the 15-months window and identify factors associated with delayed participation.

Methods: Data from the Lifelines, a population-based cohort in the north of The Netherlands, was linked to CCS-related data in PALGA (the nationwide registry of histo-cytopathology in the Netherlands) between 2001-2020. Women were included from the age of 30 till hysterectomy, death, or the age of 60. Women were categorized as timely participants and delayed participants when there was a primary screening result within 15 months or between 15-60 months after the start of the invitation year, respectively. The timely and the delayed participation rate was presented per year. The data were divided into 5-years blocks to identify the factors associated with delayed participation. For this, a multivariable logistic regression analysis was performed in each block, using age, education level, and pregnancy during the invitation year as covariates.

Results: Per year, on average, 13684 (SD:544) women in this cohort were eligible for screening. The timely participation rate was about 66% between 2001-2006, increased to 75% between 2007-2013, and started to decrease in 2014 to 69% in 2019. The delayed participation rate was approximately 5% between 2001-2013 and in 2014 began to increase to 8% in 2017. In the block 2001-2005, delayed participants were more likely to be 30-35 years old (OR,95%CI: 7.1, 5.8-8.6), be highly educated (OR,95%CI: 1.8, 1.6-1.9), and be pregnant during the invitation year (OR,95%CI: 9.5, 8.5-10.6) compared to timely participants. Similar results for age and education were found for 2006-2010, 2011-2015, and 2016-2020.

Conclusions: In Lifelines, the delayed participation in the CCS program has increased in the last five years. Considering both, timely and delayed, the participation was over 70% from 2001 to 2019. Delayed participation is associated with an age between 30-35, higher education, and pregnancy. These results might not be generalizable to the national data, and further analysis must be done to understand the low participation in recent years.

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Liang Linda
Germany

Klug Stefanie J.
Germany

#3285

REASONS FOR NON-ATTENDANCE OF COLPOSCOPY FOLLOWING AN ABNORMAL CERVICAL CANCER SCREENING RESULT IN GERMANY

25 - Colposcopy

Schauberger G[2], Fischbeck S[3], Ikenberg H[4], Blettner M[5]

[1]Epidemiology, Department of Sport and Health Sciences,Technical University of Munich, Munich, Germany

[2]Cancer Registry of Rhineland-Palatinate, Mainz, Germany

[3]Department of Psychosomatic Medicine and Psychotherapy, Medical Psychology and Medical Sociology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

[4]Cytomol MVZ, Frankfurt, Germany

[5]Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Background/Objectives: Following an abnormal screening result, colposcopy is an important step to determine disease status and guide management. Barriers exist for women to return for colposcopy, even in high-resource countries such as Germany. We described the reasons for non-attendance within a real-world screening study.

Methods: The MARZY population-based prospective cohort study collected screening data on women aged 30-65 years in Germany. These analyses were based on screening conducted at baseline (round 1) and follow-up (round 2) screening 3 years later. Screening was conducted by cytology and Human Papillomavirus (HPV) co-testing (Hybrid Capture 2). Study colposcopy referrals included abnormal cytology (atypical squamous cells of undetermined significance or worse; ASC-US+), high-risk HPV results (hrHPV) or both. Female study personnel actively recalled women by telephone who were referred to colposcopy but did not arrange an appointment within 3 months of their screen-positive result. Reasons for non-attendance were gathered during these active recall interviews and were descriptively examined.

Results: Of 2,627 women screened at round 1, 222 were referred to colposcopy and initially 106 did not undergo colposcopy. After 29 women were motivated to make an appointment, 77 (34.7%) still did not attend despite active recall. At round 2,107 of 2,093 screened were referred and 33 initially did not undergo colposcopy within the recommended time frame. After recall efforts, 23 (21.5%) still did not attend. Across both rounds, 89 did not attend colposcopy (28.9%) and among participants with low-grade cytological abnormalities or worse (LSIL+) and/or hrHPV, 55 did not attend (23.2%) despite recall efforts. 17.4% of participants positive in both tests (LSIL+ threshold) did not attend. Major reasons for non-attendance were lack of time (56.4%), barriers such as accessibility to the clinic (45.6%), and personal advice against study colposcopy by the office-based gynaecologist who conducted screening (43.9%). The majority of these women advised against study colposcopy had hrHPV only and reported having a repeat cytology test done. Almost a third of non-attendees reported that colposcopy clinic choice was limited and a quarter reported they had forgotten the appointment. Fear of the procedure or outcome of the appointment were reported in 15% of non-attendees.

Conclusions: Colposcopy attendance particularly in women with high-grade lesions needs improvement in Germany. Non-attendance can be addressed by improving patient education on screening results, and minimised by a systematic failsafe active recall component within the current screening program.

Carozzi Francesca
Italy

Carozzi Francesca Maria
Italy

#3574

QUALITY ASSURANCE IN CERVICAL CANCER SCREENING : EXTERNAL QUALITY ASSURANCE PROGRAM (EQA) FOR HPV SCREENING WITH CYTOLOGY TRIAGE AND PAP TEST SCREENING

24 - Risk management

Carozzi F[1,3], Avveduto G[2], Burroni E[3], Cannistrà S[2], Matucci M[3], Paganini I[3], Sani C[3], Terreni A[2]

[1]University of Florence, Florence, Italy
[2]Careggi Hospital, Florence, Italy
[3]ISPRO, Florence, Italy

Background/Objectives: Human papillomavirus (HPV) DNA testing has become routine in many diagnostic laboratories, particularly with changes from cervical cytology to HPV DNA as primary screening test. However, cytology continues to play a key role in HPV screening because all HPV-positive women undergo a Pap test, which in this context, is referred to as a Triage Pap test. At the same time in young women (under 30 years of age) the Pap test remains the optimal screening test. Therefore, there are currently two screening pathways differentiated by age. According to the European guidelines for quality assurance in cervical cancer screening, external quality assurance (EQA) is essential for the evaluation of laboratory performance to ensure the quality of both HPV testing and Pap testing as a triage test as well as a screening test.

Methods: In collaboration with the Tuscan Regional Center for laboratory quality assurance (Certified Accredia ISO 17043), we developed two EQA programs: one specific for screening with HPV including evaluation for HPV Test and Triage cytology and a specific program for liquid vaginal cytology only. The HPV program has been active since 2016 and the liquid phase Pap program since 2019. For HPV, the 9 samples are sent in 3 different shippings, and can be requested in either Preservcyt or Surepath but only laboratories using validated tests for screening can participate (C. Meijer et al 2009)., The corresponding Triage cytology digitalized slide, and a selection of meaningful images are made available when a positive HPV results is provided. The liquid Pap test EQA program consists of 12 digitalized cytological (vaginal??) smears (??)slides accessible on a dedicated facility.

Results: Results from both EQA programs are made available to participants within 20 days e reports are sent via e-mail. For HPV EQA, in addition to the qualitative data, semiquantitative data of HPV as well as gene housekeeping, when available in the kit used, are also analyzed. The statistical indicators are calculated as mean, standard deviation (DS) and coefficient of variation (CV) of all results arrived and according to the method used by the laboratory. Triage cytology and screening cytology are classified according to Bethesda 2014 and for each exercise it is reported: the consensus cytology interpretation ,the descriptive result sent by the laboratory, the number and percentage of results obtained from other laboratories . In addition, for screening cytology a score, based on a weighed concordance is also provided. The basic idea is to replicate the weighted Cohen's Kappa statistic principle (Cohen,1968), i.e., underlying that some discrepancies are more severe than others. The number the participating laboratories in HPV & PAP Triage EQA is increased from n. 14 in 2016 to n. 54 in 2021. In 2021, laboratories participating in the liquid phase PAP VEQ were 47 . Detailed results from both EQA programs will be presented and discussed

Conclusions: The EQA programs that we implemented for screening programs referral laboratories are open to all laboratories working in this field and focus on molecular and morphological tests used in screening for cervical cancer .To our knowledge this is the only experience in Europe and worldwide of a systematic EQA for HPV & triage cytology and screening cytology that laboratories can exploit to accomplish ISO 15189 accreditation.

Felsher Marisa
United States

Felsher Marisa
United States

#3174

ECONOMIC AND HUMANISTIC BURDEN OF HPV-RELATED DISEASE IN INDONESIA: A QUALITATIVE ANALYSIS

39 - Low resource settings

Felsher M[1,2], Setiawan D[5], Varga S[1], Della Pia R[3], Riley D[3], Newman R[3], Beveridge A[3], Oswald C[3], Kothari S[1], Postma M[2,4]

[1]Center for Observational and Real-World Evidence (CORE), Merck , Kenilworth, United states

[2]Unit of PharmacoTherapy, Epidemiology , Groningen, Netherlands

[3]Adelphi Values PROVE, Cheshire, United kingdom

[4]Department of Economics, Econometrics , Groningen, Netherlands

[5]Department of Health Sciences, University of Groningen, Groningen, Netherlands

[6]Department of Pharmacology , Surabaya, Indonesia

[7]Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia

[8]Faculty of Pharmacy, University of Muhammadiyah Purwokerto, Purwokerto, Indonesia

Background/Objectives: The global burden of human papillomavirus (HPV)-related disease(s) is increasing in developing countries, including Indonesia. However, few studies have explored how having a HPV-related disease impacts the lived experiences of adult men and women in Indonesia. Therefore, the objective of this analysis was to qualitatively explore the economic and humanistic burden of HPV-related disease(s) in patients from Indonesia.

Methods: Between June 2021 and September 2021, semi-structured interviews were conducted with patients diagnosed with a HPV-related disease (genital warts or cancer), identified from a range of clinical settings in Jakarta, Indonesia and surrounding regions. Clinical settings included government mandated primary care clinics and hospitals providing specialist care, such as ear nose and throat specialists, urologists and gynecologists. For further insight, health care professionals (HCPs) specialized in treating HPV-related disease(s) were also recruited for a separate semi-structured interview. This research received ethical approval from the ethical committee at Muhammadiyah Purwokerto University. Thematic analysis of qualitative interviews was used to explore the impact of HPV-related disease(s) on finances, social relationships, physical and mental health.

Results: Eighteen patients were recruited (nine men and nine women), aged 30-56 years. Patients had head/neck cancer (n=8), anogenital cancer (anal, penile, or vaginal cancers; n=4), cervical cancer (n=3), or genital warts (n=3). Ten HCPs were also recruited. Patients most frequently emphasized the humanistic burden of their HPV-related disease(s), particularly surrounding the negative impact on their emotional and mental state, and relationships with friends and family. The overall cost of HPV-related disease(s) caused a severe economic burden for patients. Patients reported alterations in physical ability and productivity due to their disease(s), leading to low or reduced income. HCPs mostly emphasized the financial impact of HPV-related disease(s) and consistently understated the emotional and societal burden of disease.

Conclusions: Patients described various ways in which HPV-related disease(s) negatively impacted their lives. There was evidence of a substantial economic burden, but the largest emphasis was on mental and social health. This research highlights the need to identify ways to reduce the negative psychosocial consequences of HPV disease(s) in Indonesia. Furthermore, increased HCP education of the broader humanistic impacts of HPV-related disease(s) may help them best support their patients.

Vahteristo Maija
Finland
Vahteristo Maija
Finland

#3383

Searching for optimal algorithms for primary HPV screening

12 - Triage of HPV positive women

Vahteristo M[1]

[1]Finnish Cancer Registry, Helsinki, Finland

Background/Objectives: Primary HPV screening programmes have been implemented in many European countries. Currently many of these screening programmes suffer from overdiagnosis and high colposcopy burden. Our goal was to identify the key characteristics of various algorithms for the management protocols for primary HPV screening with cytology triage, based on the Finnish HPV implementation trial with over 20-year follow-up.

Methods: Using the HPV implementation trial data, we formulated post-hoc 6 different algorithms for HPV screening (HPV 1 - 6) and one for cytology screening. We combined these data with all the CIN II+ cases registered during this trial. Sensitivity, specificity, and colposcopy referral rate for CIN II+ detected during the first and second screening round were calculated for the algorithms.

Results: Results are presented in a picture provided as a supplementary file.

Conclusions: Almost all the HPV algorithms were superior in the CIN II+ sensitivity compared to the cytology algorithm which has a high effectiveness in Finland. The results were consistent in the first and second screening rounds of the trial. In HPV algorithms, the return of HPV positives back to the routine screening at any stage of the screening round will reduce the sensitivity of the screening. To achieve algorithms for primary HPV screening with both low colposcopy burden and good sensitivity, other triage methods than cytology are needed.

Carozzi Francesca
Italy

Carozzi Francesa Maria
Italy

#3654

HPV screening in Bolivia: results by a Pilot study

39 - Low resource settings

Carozzi F[1], Royder Yanez R[2], Cannistrà S[1], Matucci M[1], Paganini I[1], Sani C[1], Von Borries S[1], Traina S[2]

[1]ISPRO, Firenze, Italy

[2]AICS, La paz, Bolivia

Background/Objectives: Cervical cancer is a major public health problem in Bolivia.Little is known about the prevalence of HPV infections in the Bolivian population and therefore about the feasibility of a screening program based on HPV and self-sampling.In 2019, the Italian Agency for Development Cooperation (AICS), La Paz regional office. conducted a pilot study to estimate the prevalence of High-risk human papillomavirus (hr-HPV) and the feasibility of HPV screening in Bolivia, using self-sampling and portable & Transportable lab Units for HPV test in urban and rural districts

Methods: The project enrolled women 20-65 age in 3 different area: La Paz City, Toro Toro andAcasio (rural centers). Self-sampling was carried out with Viba-Brush® system and preservation in Thinprep® containers. We used Gene Expert system for HPV HR that detects E6/E7 of 14 HPV types in Real Time PCR a system of easy execution with minimal manual intervention of the operator. The system provides the results in about 1h. Women testing positive for any HPV 16 or HPV 18/45 returned for colposcopy while women positive for other HR types performed cytology triage and if Pap test was positive women are referred to Colposcopy.Enrollment began in December 2019 and lasted until June 2021. Enrollment was particularly challenging as the period coincided with the COVID-19 pandemic and follow-up test retrieval is still ongoing.

Results: 2201 subjects were enrolled of which 811 (36.84%) in Acasio, 622 (28.26%) in La Paz and 768 (34.89%) in Toro Toro. Samples with valid HPV test (neg/pos for HPV) were 2076 (94.31%). Total positivity to hr-HPV was 12.72% with a classical trend by age. The two rural areas show lower positivity than women enrolled in the city (15.31% in La Paz, 10,57% in Acasio and 12.89%. in Toro Toro; RR urban vs rural:1.4; 95%CI:1.04-1.80)). The overall data from the 3 municipalities show that the highest frequency group is HPV 31/33/35/52/58, followed by HPV 39/56/66/68, HPV 51/59, HPV 16and HPV 18/45, finding in part already reported in 2 previous Bolivian studies, despite the very low number of enrolled women.The number of colposcopies performed on screening cases is low and we are trying to retrieve them. However, from currently available data, the high-grade lesions are all related to HPV 16 or HPV18/45, single or in co-infections with other HR-HPV

Conclusions: Prevalence of HR HPV infection, measured with a validated test for screening, showed total and by age estimates comparable to the ones observed in Europe and USA. This finding confirmed 1) the feasibility of applying a screening protocol based on HPV test with self-sampling and 2) the high prevalence of cervical cancer in Bolivia is likely related to the lack of screening programs, not to a higher occurrence of Hr-HPV infections. We adopted a screening system with pre-prepared cartridges that requires minimal intervention by the operator. Performing HPV tests locally allows to avoid the problems of transport and storage of the material collected, the possibility of having the woman waiting in the clinic for the test response of the negative screening test in an hour. In positive cases, the staff scheduled an appointment for the pap test or colposcopy, depending on the type of HPV present. Sustainability of HPV testing is certainly still a major problem. The cost is about 15 euros, too high for low-income nations. A joint action between the national scientific community, international institutions and manufacturers is needed.

Sláma Jiří
Czech Republic

Sláma Jiří
Czech Republic

#3761

FINAL DATA FROM LIBUSE TRIAL - ALGORITHM FOR CERVICAL CANCER SCREENING IN THE CZECH REPUBLIC WITH USAGE OF HPV DNA TESTING WITH HPV 16/18 GENOTYPING AND P16/KI-67 DUAL-STAINED CYTOLOGY

10 - HPV screening

Sláma J[1], DvoŘák V[2], Trnková M[3]

[1]General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech republic

[2]Center of Primary Care, Brno, Czech republic

[3]Department of Pathology, Aesculab, Prague, Czech republic

[4]G-Center, Olomouc, Czech republic

Background/Objectives: The incidence and mortality rates of cervical cancer in the Czech Republic have remained unchanged for more than 30 years regardless of the existing national screening based on annual Pap smear. The aim of our prospective study was to evaluate the role of HPV DNA testing with 16/18 genotyping and p16/Ki-67 immunocytochemical triage.

Methods: Women aged 30 to 60 years who underwent routine annual Pap smears at 12 collaborating centers were tested for HPV DNA with the addition of selective 16/18 genotyping (Cobas 4800, Roche) at 3-year intervals. All HPV 16/18-positive cases and/or cases with severe abnormal cytology were sent directly to colposcopy; HPV non-16/18-positive cases and LSILs were triaged using p16/Ki-67 dual-stain cytology (CINtec Plus, Roche) and positive cases were referred to colposcopy.

Results: Altogether 2407 patients were eligible for analysis. The mean age of the subjects was 43 years. Twelve cases with severe Pap smear abnormalities were identified throughout the study period. A total of 7.4% (180/2418) patients were found to be HPV positive and 5.4% were HPV positive at the end of the study, 2% were HPV 16/18 positive at baseline and 1.1% were HPV positive at the end of the study. Triage using p16/Ki-67 was positive in 22.5% of cases (29/129). After 3 years of follow-up, biopsy confirmed 51 HSILs and 2 glandular lesions, all of which were HPV positive.

Conclusions: Screening based on HPV testing with selective 16/18 genotyping and p16/Ki-67 triage demonstrated four times more high-grade lesions, including glandular lesions, than standard Pap smear-based screening over 3 years. After three years, there was a significant reduction in HPV positivity, HPV 16/18 positivity, high-grade lesions, and referral for colposcopy.

Tisler Anna
Estonia

Tisler Anna
Estonia

#3283

WOMEN'S RIGHT TO LIFE IS NOT AGING, OLDER WOMEN HAVE TO BE SCREENED FOR CERVICAL CANCER

10 - HPV screening

Tisler A[1], Pärna K[1], Uusküla A[1]

[1]University of Tartu, Tartu, Estonia

Background/Objectives: Estonia is a European Union country experiencing high cervical cancer mortality (4.3 / 100 000) and incidence (18.5 / 100 000) rates in 2020 despite having organised screening program from 2006. Inadequate uptake, insufficient quality of the Pap-smear based screening, and stage distribution shifting towards later stages are described before. Importantly, cervical cancer screening is targeting women up to 65 years. In 2020, 31% of incident cervical cancer cases in Estonia were reported among women >=65. High-risk HPV infection is a necessary cause for cervical cancer. The purpose of the study was to determine a population-based HPV prevalence and to describe sociodemographic and sexual behavioral patterns among women wide age range in Estonia.

Methods: A random age stratified (30-33, 57-60, 67-70) study sample comprised 3065 women representing Estonian female population. All women were invited to the study from October 2020-May 2021 using e-mail or paper invitation. Each participant or those who did not react on invitation was sent a package containing a (self-sampling) vaginal swab collection kit (Eswab, Copan), collection instructions, informed consent and questionnaire on sociodemographic, reproductive history, sexual behaviour and healthcare utilization data. HPV genotyping was made using Luminex xMAP (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82).

Results: Filled out questionnaires and samples were returned from 1347 (44%) targeted sample. Prevalence of any type of HPV infection was 19%. We observed a U-shape prevalence curve - with hrHPV prevalence of 22%, 15%, and 19% among women aged 30-33, 57-60 and 67-70 respectively. The most common HPV types detected in study population were HPV 53 (19%), 56 (16%) and 16 (14%); among older women HPV 68 (33%) and HPV 53(29%). 20% and 34% of women aged 67-70 have not been screened for the last five and three years respectively. High proportion of older women did not have higher education (60%), were having unprotected sex during their first sexual intercourse (70%) and a quarter reported being currently sexually active.

Conclusions: To our knowledge this is the largest assessment of HPV prevalence in Estonian female population. The overall HPV prevalence in our study population was high and documents a high prevalence of hrHPV among older women (aged >65) currently excluded from screening. However, these older women are at continuous risk for cervical cancer. Discontinuing screening at age 65 is premature and extension of screening age span in older age is warranted.

FC05 - Methylation

De Waard Jolien
Netherlands

De Waard Jolien
Netherlands

#3652

CIN3+-specific methylation marker analysis to improve the triage of hrHPV-positive self-samples in the population-based cervical cancer screening

18 - Methylation

De Waard J[1], De Boer M[1], Bhattacharya A[2], Vermeulen K[3], De Bock T[3], Schuuring E[4], Wisman B[1]

[1]Department of Gynaecologic Oncology, University Medical Centre Groningen, Groningen, Netherlands

[2]Department of Medical Oncology, University Medical Centre Groningen., Groningen, Netherlands

[3]Department of Epidemiology, University Medical Centre Groningen, Groningen, Netherlands

[4]Department of Pathology, University Medical Centre Groningen , Groningen, Netherlands

Background/Objectives: The current Dutch population-based screening (PBS) programme for cervical cancer consists of primary high risk human papilloma virus (hrHPV) testing with cytology as triage test on cervical scrapings. Material is collected by a general practitioner (GP) or by the woman herself using a self-sampling device. One disadvantage of the self-sampling device is that hrHPV-positive women need to visit their GP to determine whether referral for a colposcopy is needed, as cytological examination is not possible on self-collected material. This will result in delay of the correct diagnosis and less compliance to the PBS. These drawbacks may be circumvented by direct molecular triage testing using hrHPV-positive self-samples. Previously, we have reported that methylation marker analysis is feasible for molecular triage testing. The aim of this study is to determine the most optimal methylation marker panel to detect CIN3+ in hrHPV-positive self-sampled material.

Methods: We selected 23 methylation markers based on literature with high sensitivity and specificity for CIN3+ status (>70%) using GP-collected scrapings. Quantitative methylation-specific PCR (QMSP) was set up and performed on bisulfite treated DNA of 208 hrHPV-positive self-samples of women with a CIN2 or less (controls) and 96 women with CIN3 or worse (cases). Receiver operating characteristic (ROC) was performed to analyse the diagnostic performance by calculating the area under the curve (AUC), sensitivity and specificity.

Results: QMSP analysis of these individual markers showed discriminative DNA methylation levels between controls and cases in all markers ($p<0.05$). ROC analysis for CIN3+ showed that 10/23 markers had an AUC of >0.7 ($p<0.001$). For 7/23 markers, sensitivity was >60% with a specificity of >70% for CIN3+.

Conclusions: Our study established promising methylation markers to be used in hrHPV-positive self-sampled material as putative triage test. To improve sensitivity, various methylation markers are presently combined to identify a panel with the highest combined sensitivity and specificity using cluster analysis and decision tree modelling. An external validation of this optimized panel will be performed in a large cohort of 2415 hrHPV-positive self-samples.

Schmitz Martina
Germany

Hums Anna-bawany
Germany

#3692

Clarification testing/triage of women tested HPV DNA-positive in cervical cancer screening using a DNA methylation marker-based test as well as an HPV mRNA test

15 - Molecular markers

Campana G[2], Knoll K[1], Schuster C[2], Zimmermann-marroquin J[2], Schmitz M[1], Hansel A[1], Hums A[1]

[1]oncgnostics GmbH, Jena, Germany

[2]Medizinisches Versorgungszentrum für Gynäkologie, Zytologie, Pathologie und Laboratoriumsmedizin GmbH, Wasserburg, Germany

Background/Objectives: HPV-testing is more and more implemented in cervical cancer screening, due to its higher sensitivity compared to cytology. As HPV screening is less specific, however, reliable triage methods are essential in such a setting in order to avoid overtreatment and higher screening costs. DNA methylation markers may provide a suitable tool especially with respect to keeping false-positive rates low. GynTect® is a DNA methylation assay using six human genomic marker regions, ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671. It's utility in screening triage was assessed, especially in comparison to HPV mRNA testing.

Methods: Cervical smear samples from 231 women with cytology findings ≥Pap III, collected in a new liquid-based cytology medium (BestPrep®; CellSolutions), were selected for the study. For all samples results from HPV DNA testing (Roche Cobas HPV test) were available. For the study, HPV mRNA testing was performed using the Aptima HPV test (HOLOGIC). Testing for the six DNA methylation markers comprising GynTect was performed for all samples following the instructions of the supplier.

Results: The overall positivity for both tests within this cohort was higher for HPV mRNA than for GynTect (155 vs. 86 samples). Regarding cytology, 170 of the 231 cervical smear samples fell into the Pap III group, 53 into the Pap IV group, and 8 into the Pap V group. For both tests, positivity was significantly lower in the Pap III group than in the Pap IV group (HPV mRNA 64% vs 85%; GynTect 24% vs 81%). Of the 231 samples 33 were from women tested HPV DNA-negative, 94 were from women at least positive for one of the HPV types 16 or 18, and 104 samples were from women positive for any of the other 12 high-risk HPV types. Of the 33 HPV-negative samples, five were positive for HPV mRNA, and six were positive for GynTect. Two of the samples were positive for both tests. Among the 94 samples being HPV16 and/or HPV18-positive, 70 contained HPV mRNA, and 57 were GynTect-positive. Concordant positive results for both tests were obtained for 51 samples. Among the 104 samples with (at least) one of the other 12 high-risk HPV types, 80 were positive for HPV mRNA, whereas only 23 were positive for GynTect. Of these, 22 were also HPV mRNA-positive. The remarkable difference between HPV mRNA positivity and GynTect positivity in this group is mainly seen within those samples that showed a Pap III cytology. Of these 90 samples, 68 (75.6%) were HPV mRNA-positive, whereas only 12 (13.3%) were GynTect-positive. 11 of these 12 GynTect-positive samples were also HPV mRNA-positive.

Conclusions: Detection of mRNA of the HPV oncogenes E6 and E7 provides a sign for a persisting infection with HPV and thus a higher risk of the patient for developing a high-grade cervical lesion. In contrast, the DNA methylation markers comprising GynTect are a direct sign for carcinogenesis. Therefore, it is not too surprising that triage using GynTect may show much higher specificity than using HPV mRNA. Interestingly, the main difference in positivity of both tests is seen in the group of samples that are HPV DNA-positive and show a cytology Pap III. Thus, GynTect may help to clarify the malignancy status of HPV-positive women with cytological signs of max. mild dysplasia.

Zhang Mengzhen
China
Zhang Mengzhen
China

#3687

CLINICAL SIGNIFICACE OF METHYLATED ZNF582 AS A TRIAGE MARKER FOR HR-HPV INFECTED WOMEN

18 - Methylation

Zhang M[1]

[1]13683806877@163.com, Zhengzhou, China

Background/Objectives: The aim was to investigate the value of the methylated genes and cytology as shunt in hr-HPV infected women, especially in women with cervical transformation zone III (TZ III).

Methods: Total of 204 patients infected with hr-HPV were enrolled in this study from the First Affiliated Hospital of Zhengzhou University. Cervical exfoliated cells were collected for liquid-based cytology (LBC) and ZNF582 / PAX1 methylation (ZNF582m / PAX1m) tests before the colposcopy and biopsy. All enrolled patients were divided into normal/cervicitis (n=59), CIN1 (n=42), CIN2 (n=38), CIN3 (n=40), and cervical cancer groups (n=25) according to pathological results.

Results: In the hr-HPV infected women, the sensitivity / specificity of ZNF582m, PAX1m and LBC tests for detecting CIN3 + were 70.2% / 89.9% , 58.4% / 87.8% and 70.8% / 60.4%, respectively. The sensitivity of the ZNF582m and LBC tests for CIN3+ were significantly higher than PAX1m test ($p<0.05$) and the specificity of the ZNF582m and PAX1m tests for CIN3+ were significantly higher than LBC test ($p<0.01$). In the hr-HPV infected women with TZ III, the sensitivity of ZNF582m and PAX1m for detecting CIN3+ were 88.5% and 69.3%, which were similar to that (80.8%) of LBC ($p>0.05$), and the specificity of ZNF582m and PAX1m were 90.9% and 88.3%, which were significant higher than that (57.1%) of LBC ($p<0.01$).

Conclusions: The ZNF582m test was a promising triage marker for the hr-HPV infected women in China, which was superior than LBC and PAX1m tests.

References: none

Floore Arno
Netherlands

Floore Arno
Netherlands

#3705

STREAMLINED WORKFLOW FOR METHYLATION ANALYSIS ON CERVICAL SAMPLES

18 - Methylation

Floore A[1], Arno F[1]

[1]Self-screen BV, Amsterdam, Netherlands

Background/Objectives: Triage testing of HPV-positive women by methylation analysis to select women with (pre)cancerous lesions that need colposcopy is emerging. Methylation detection assays usually require pretreatment of the sample DNA with sodium bisulfite conversion to separate methylated from unmethylated cytosines. Streamlined workflows for this pretreatment that comply with the needs of laboratories for high-throughput testing are needed.

Methods: This study evaluated a direct cell conversion protocol on cervical samples in PreservCyt as alternative to isolated genomic DNA as input. The direct conversion protocol is capable of handling 96 samples simultaneously (manually or automated). Clinician-collected cervical samples (n = 120) were subjected to a direct conversion protocol, or genomic DNA was isolated with a fixed amount used for subsequent bisulfite conversion. Converted samples were compared for ACTB control gene and methylation of FAM19A4 and miR124-2 genes using quantitative methylation-specific PCR (QIAsure Methylation Test).

Results: Direct conversion resulted in a high success rate, i.e., 119/120 (99.2%) samples reported a valid test result. ΔΔCq values of FAM19A4 and miR124-2 were significantly correlated between both protocols (Spearman Rho 0.708 and 0.763, respectively).

Conclusions: A direct cell conversion protocol shows good technical and analytical performance and offers a streamlined workflow for methylation analysis.

Schmitz Martina
Germany

Hansel Alfred
Germany

#3604

DNA methylation markers for the detection of VIN, VAIN and vulva or vagina carcinoma

27 - Vulvar diseases and neoplasia

Wunsch K[1], Hansel A[1], Petzold A[2], Dürst M[2], Schmitz M[1], Runnebaum I[2]

[1]oncgnostics GmbH, Jena, Germany

[2]Department of Gynaecology, Jena University Hospital, Jena, Germany

Background/Objectives: Vulvar and vaginal cancers together accounted for 1.3% of the global cancer incidence among women in 2020. The majority of vaginal cancers and a lesser proportion of vulvar cancers are associated with HPV. Rising incidence rates of vulvar cancer are observed especially in developed countries, and these seem to be mainly attributable to high-risk HPV-positive cases in younger women. Currently, no organized screening is performed in any country, so early detection is often an incidental finding during routine visit at the gynecologist. We analyzed the DNA methylation marker panel comprising GynTect, a CE IVD-marked assay for use in cervical cancer diagnostics, on vulvar and vaginal scrapes from women with vulvar and vaginal disease.

Methods: Scrapes from 43 patients, mean age 64, with vulvar (n=37) and vaginal (n=6) carcinoma as well as 25 vulvar intraepithelial neoplasias (VIN) and 8 vaginal intraepithelial neoplasias (VAIN) of different severity grade (17 VIN3, 5 VIN2, 3 VIN1 and 4 VAIN3, 3 VAIN2 and 1 VAIN1, mean age 58) were analyzed using GynTect, a DNA methylation marker assay comprising CpG islands in the promoter/5' regions of the human genes ASTN1, DLX1, ITGA4, RXFP3, SOX17 and ZNF671. Of the 25 VIN, 21 were HPV positive and 4 were HPV negative. All 8 VAINs were HPV-positive. Of the 37 vulvar carcinoma, 21 were HPV negative, whereas 16 were HPV-positive. All 6 vaginal cancers were HPV positive.

Results: Of the 33 VIN/VAINs, 21 (63.6%) were above the score defined for a GynTect positive. The 4 HPV-negative VINs were also GynTect-negative. All samples with a positive GynTect score were among the HPV positive samples, overall GynTect detection was 72.4% (21 of 29 samples) with a higher proportion of positively tested samples in the VIN group (17 of 21 samples; 80.9%). All 6 vaginal carcinoma cases (all HPV-positive) were GynTect-positive. Of the overall 37 vulvar cancers 28 showed a positive GynTect score. Of the 16 HPV-positive vulvar cancer scrapes, 15 (93.8%) were detected with GynTect, and of the 21 HPV negative cases, 13 (61.9%) showed a positive GynTect score.

Conclusions: As an increasing proportion of vulvar and vaginal cancer and their precancerous lesions are associated with high-risk HPV infection, we tested whether the six DNA methylation markers comprising the cervical cancer diagnostic GynTect, may be useful in diagnostics of these diseases as well. Interestingly, a high proportion of the samples were positive for GynTect, partially irrespective of the HPV status. Thus, in combination with HPV diagnostics, DNA methylation testing with these markers might be a promising tool for early detection of malignant vulvar or vaginal disease.

Boers Joachim
Netherlands

Joachim Boers
Netherlands

#3534

THE PROOF-OF-PRINCIPLE OF MARKER DISCOVERY FOR DIFFERENT GYNECOLOGICAL CANCERS BY A NOVEL METHOD FOR GENOME-WIDE DNA METHYLATION PROFILING (MED-SEQ)

18 - Methylation

Joachim B[1,2], Ruben B[1,2], Wilfred V[1,2], Henk V[2], Joost G[1,2], Wim Q[2]

[1]Erasmus University Medical Center , Rotterdam, Netherlands
[2]Methylomics, Rijswijk, Netherlands

Background/Objectives: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer, is applied to classify tumors and can predict disease outcome and treatment options.

Methods: We developed a novel method that facilitates genome-wide methylation marker discovery allowing successful identification of methylation changes associated with pre-cancer and cancer at very low cost. The assay involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE) or fresh biopsies (only 10-50ng DNA is needed). A DNA methylation dependent restriction enzyme digestion releases 32 base pair DNA methylated fragments that are sequenced by next generation sequencing. This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing detection of DNA methylation at more than 50% of the 30 million CpGs present in our genome. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no DNA bisulphite treatment. MeD-seq is compatible with low amounts of DNA derived from solid tumor tissue enriched by laser capture microdissection (LCM) and liquid biopsies.

Results: We compared MeD-seq profiles of different types of cancers from vulva, cervix, endometrium, fallopian tube and ovary between cancers vs controls and cancers vs other cancers. Identification of Differentially Methylated regions (DMR) was achieved by comparing MeD-seq profiles using genome wide statistical testing using a sliding window approach, visualized through the Integrative GenomicsViewer (IGV) and subsequent identification of primer and probe regions for quantitative Methylation-specific PCRs (qMSP) to detect tumor-specific or general-tumor markers. In addition to DNA methylation data, MeD-seq generates sequencing data which enables the detection of Human Papilloma Virus (HPV) DNA incorporated in the genome of HPV-infected cells. Around half of the gynecological cancer types in our study are HPV-associated and we were able to detect HPV genomic integration and call HPV subtypes based on MeD-seq data.

Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation profiles of FFPE treated laser dissected material of cancer and controls and can be used to call DMRs for development of PCR-based assays. In addition to interrogating genome wide DNA methylation, MeD-seq is able to detect HPV integration in host genomes and able to call specific HPV subtypes.

Schmitz Martina
Germany

Schmitz Martina
Germany

#3720

GynTect DNA methylation marker - longitudinal observational study in patients with CIN2/3. Results from the GynTect-PRO trial

18 - Methylation

Schmitz M[1], Wunsch K[1], Hansel A[1], Hippe J[1], Heller T[3], Hoyer H[4], Dürst M[2]

[1]oncgnostics GmbH, Jena, Germany

[2]Department of Gynaecology, Jena University Hospital, Jena, Germany

[3]Center for Clinical Studies (ZKS), Jena University Hospital, Jena, Germany

[4]Institute for Medical Statistics, Informatics and Data Science, Jena University Hospital, Jena, Germany

Background/Objectives: Precancerous lesions of the cervix, depending on their grade of severity, are known to have a high potential to regress to normal. Especially among young women, only a few patients are at high risk to develop invasive cancer. Up to now, current methods are not able to distinguish between high risk patients and those patients who are likely to show regression of their precancerous lesions. DNA methylation markers such as the CpG islands in the promoter regions of the genes ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671 comnprising the diagnostic test GynTect® are a new class of biomarkers which are discussed to have prognostic potential. GynTect-PRO is a prospective, longitudinal and multi-centered trial in Germany aiming to address the probability of regression in GynTect-negatively tested women having a CIN2 or CIN3 lesion (Negative Predictive Value, NPV). The study tests the null hypothesis NPV≤70% against the alternative hypothesis NPV≥90%.

Methods: 77 women <25 years were included between December 2017 and February 2021, recruited from nine clinical centers in Germany. All patients had a histopathology confirmed CIN2 or CIN3 lesion at first visit. Follow-ups were planned for all patients every 6 months. CIN2 patients were observed for up to 24 months (a max. of 5 visits) and CIN3 patients for up to 12 months (a max. of 3 visits). At all visits, colposcopy was done and, if indicated, a biopsy was taken. HPV testing, cytology and GynTect testing was also done at every timepoint. The outcome was defined as progression, persistence or regression with respect to the last biopsy, conization or colposcopy findings if no histopathology was done at the last visit. In the end, 60 women fulfilled all inclusion criteria.

Results: In total, 18 of 24 CIN2 and 27 of 36 CIN3 patients had a negative GynTect result at the study entry point. Over time, 12 of 18 GynTect negative CIN2 patients showed regression (NPV=67%, 90%CI 44%-85%), whereas 5 persisted during the follow-up period (2 of them with follow-up <1.5 years). One patient showed progression. Of the 27 GynTect negative CIN3 lesions 15 regressed (NPV=56%, 90%CI 38%-72%) and 12 showed persistence (5 of them with follow-up <0.8 years). 4 CIN2 and 6 CIN3 were tested GynTect positive and 2 CIN2 and 3 CIN3 showed an invalid result at entry point.

Conclusions: The objective of the study to show a negative predictive value of ≥90% for a GynTect negative result was missed. Since follow-up of some patients was shortened the probability of a final regression could be underestimated and that of a final persistence overestimated. On the other hand, regression of a lesion may be induced by repeated biopsies taken for safety reasons during follow-up. For valid NPV estimates we need to study the natural development of CIN2/3 lesions over a relevant period, a task which is difficult to implement in the target clinical setting.

Li Lei
China

Chao Xiaopei
China

#3680

Novel methylated genes as a clinical predictor to reduce the missed diagnosis of cervical lesions (cancer) in women over 50 years old: a preliminary analysis of a multicenter study

18 - Methylation

Chao X[1], Li L[1], You Y[2], Wu H[2]

[1]Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Beijing, China

[2]Department of Pathology, Peking Union Medical College Hospital, Beijing, China

Background/Objectives: Women over 50 years old have a higher risk of cervical lesions (cancer) than young population, but account for the majority of cervical missed diagnosis by three-step examination. Only a few articles pointed out non-invasive methods to reduce the missed diagnosis in postmenopausal women. Objectives: The main purpose of the study is to analyze whether the CisCer methylation genes (PAX1 & JAM3) can be as the new non-invasive method to increase the accuracy of cervical cancer diagnosis.

Methods: From 2019 to 2022, a prospective study of outpatient opportunistic cervical cancer screening was conducted in three hospitals with multiple centers. More than 20,000 subjects will be collected and all subjects will be follow-up for one year. The research team of Peking Union Medical College Hospital is responsible for preliminary experiment, clinical study planning, and process quality control. Cervical exfoliated cell specimen was collected and analysis for the system setup including SOP of sample collection, quality of specimen, and experimental operation. The analysis of methylation level was determined by using CisCer methylation real-time system (CISPOLY Co., China).

Results: A system set-up study was conducted on 905 subjects including normal uterine cervix (n=501), CIN1(n=170), CIN2(n=69), CIN3/CIS(n=110), SCC (n=15), and adenocarcinoma (n=17) of the uterine cervix diagnosed according to histological results. The sensitivity and specificity of CisCer methylation were 82% and 88% in all subjects and 87% and 86% in subjects over 50 years old compared with HPV16 / 18 (74% and 72%) and LBC (ASCUS; 96% and 24%). The cancer missed diagnosis rates of cancer of CisCer, HPV16 / 18, LBC (^{3}ASCUS), and LBC (^{3}LSIL) in women over 50 years old were 0%, 18%, 6%, and 29%, respectively.

Conclusions: The preliminary results indicated that the CisCer real time PCR-based testing is promised for cervical cancer detection with high sensitivity and specificity without cancer missed diagnosis for women over 50 years old.

FC06 - Epidemiology, natural history and public health 1

Thomsen Louise T.
Denmark

Thomsen Louise T.
Denmark

#3600

HPV PREVALENCE ACCORDING TO SOCIOECONOMIC CHARACTERISTICS IN A DANISH SCREENING POPULATION

03 - Epidemiology and natural history

Thomsen L[1], Sand F[1], Oernskov D[2], Munk C[1], Waldstroem M[2,3], Kjaer S[1,4]

[1]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark

[2]Department of Pathology, Vejle Hospital, Lillebaelt Hospital, Region of Southern Denmark, Vejle, Denmark

[3]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

[4]Department of Gynecology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Background/Objectives: The Danish health care system is based on a principle of free-of-charge access for all residents, and nationwide cervical cancer prevention programs have been implemented. Nevertheless, social inequality is seen in cervical cancer incidence and mortality, with higher rates in women who have basic education, are unemployed or have low income. It is unknown whether there are also socioeconomic differences in the prevalence of HPV. The aim of this study was to investigate the prevalence of high-risk (hr) HPV according to socioeconomic characteristics in a Danish screening population.

Methods: We used data from a large pilot implementation of HPV-based cervical cancer screening. During May 2017-December 2020, women aged 30-59 years screened in the uptake area of the Dept. of Pathology, Vejle Hospital, Region of Southern Denmark, were offered primary HPV testing or primary cytology depending on municipality of residence. In the HPV group, ThinPrep liquid-based cytology samples were tested with the Cobas® HPV test. Using each woman's personal identification number, we obtained registry information on HPV vaccination and socioeconomic characteristics, including educational level, employment and country of birth. We calculated the hrHPV prevalence according to age and socioeconomic characteristics, and used log-binomial regression to estimate the relative prevalence (RP) of hrHPV infection, adjusted and stratified for age.

Results: We included 36,419 women with a valid HPV result. The majority (85%) were HPV unvaccinated, and those vaccinated had received the quadrivalent vaccine as adults (median age at vaccination: 26 years, range 17-57). The hrHPV prevalence decreased with age (30-39 years: 11.2%; 40-49 years: 8.0%; 50-59 years: 6.2%). Among women aged 30-39, the hrHPV prevalence was higher in those with basic compared with long education (12.8% vs 10.3%; RPage-adjusted=1.24; 95% CI, 1.06-1.45) and in women who were unemployed compared to employed (12.6% vs 10.8%; RPage-adjusted=1.13; 95% CI, 1.00-1.28). Immigrants from non-Western countries had lower hrHPV prevalence than Danish-born women (8.7% vs 11.5%; RPage-adjusted=0.76; 95% CI, 0.63-0.90). Similar patterns were seen in women aged 40-49 and 50-59 years.

Conclusions: In this largely unvaccinated Danish population, we found socioeconomic disparities in hrHPV prevalence, with higher prevalence in women with basic education and unemployment, and lower prevalence in non-Western immigrants. This may be caused by different sexual behavior patterns. Our findings support the need for promoting HPV vaccination and cervical cancer screening in socioeconomically challenged groups.

Tanaka Luana
Germany

Tanaka Luana F.
Germany

#3577

SMEAR HISTORY OF WOMEN WITH CERVICAL CANCER: AN AUDIT OF ROUTINELY COLLECTED SMEARS IN THE TEQAZ STUDY

03 - Epidemiology and natural history

Tanaka L[1], Ikenberg H[2], Klug S[1]

[1]Chair of Epidemiology - Department of Sport and Health Sciences - Technical University of Munich, Munich, Germany
[2]MVZ für Zytologie und Molekularbiologie Frankfurt GbR (CytoMol), Frankfurt, Germany

Background/Objectives: From 1971, Germany offered an opportunistic cytology-based cervical cancer screening for women aged 20 years and older. In 2020, Germany switched to an organised cervical cancer screening programme, with women aged 20 to 34 years receiving cytology-based screening and those aged 35 years and older undergoing HPV-cotesting. Non-participation in screening is a major risk factor for cervical cancer, but some women who frequently participated in cytology-based cervical cancer screening still develop cervical cancer, which could indicate quality issues in cytology. The aim of this study was to analyse the smears history of women who developed cervical cancer screening (cases) in the TeQaZ case-control study.

Methods: TeQaZ is a case-control study on cervical cancer and participation in screening and quality of cytology. We recruited women with newly diagnosed cervical cancer (ICD-10 C53) and population-based controls between 2012 and 2016. We retrieved the smears collected and their results (routine assessment) in the ten years before diagnosis (cases) or study entry (controls) and sent them for an audit performed by an independent cytologist (first review). A second independent cytologist reviewed the smear in case of disagreement between the routine assessment and the first review. Independent cytologists were blinded to the routine assessment. For the present analysis, we selected cases for whom at least three smears were retrieved and reviewed.

Results: Thirty-two cases had at least three smears collected within the ten years preceding diagnosis, contributing with more than 150 smears for the audit. Most were diagnosed with squamous cell carcinoma and small tumours (T1). The median age at study recruitment was about 41 years. Almost half of women had received at least one false negative result, with some women having multiple smears incorrectly classified. A considerable proportion of women had only normal smears in the years preceding cervical cancer diagnosis, with some only receiving the first positive test, which led to cervical cancer diagnosis.

Conclusions: Our analyses of routinely collected smears of women who developed cervical cancer indicate issues with a high proportion of cases who had received at least one false negative result and with a considerable proportion of cases with no history of abnormal smears preceding a cervical cancer diagnosis. Considering that cytology will remain an important part of the screening and remains the method of choice for women aged 20 to 34 years living in Germany, strategies to improve cytology quality should be implemented.

Gillis Jennifer
Canada

Gillis Jennifer L.
Canada

#3657

SELF-REPORTED PARTICIPATION IN CERVICAL CANCER SCREENING AMONG A VOLUNTEER COHORT OF VACCINATED WOMEN IN BRITISH COLUMBIA, CANADA

40 - Public health

Gillis J[1,2], Donken R[5], Marty K[2], Racey C[1,3], Smith L[1,8], Mitchell-foster S[1,6], Dawar M[12], Krajden M[4], Naus M[4], Van Niekerk D[8], Dobson S[1], Dionne M[9], Sauvageau C[9], Gilca V[9], Mayrand M[10], Money D[1,3], Kellner J[11], Sadarangani M[1,2], Ogilvie G[1,3]

[1]Faculty of Medicine, University of British Columbia, Vancouver, Canada

[2]Vaccine Evaluation Center, BC Children's Hospital, Vancouver, Canada

[3]Women's Health Research Institute, BC Women's Hospital, Vancouver, Canada

[4]BC Centre for Disease Control, Vancouver, Canada

[5]Department of Epidemiology and Data Science, Amsterdam University Medical Centers, Amsterdam, Netherlands

[6]University of Northern British Columbia, Prince george, Canada

[7]Vancouver Costal Health Authority, Vancouver, Canada

[8]BC Cancer, Vancouver, Canada

[9]Social and Preventive Medicine Department, Laval University, Quebec city, Canada

[10]Department of Obstetrics-Gynecology, University of Montreal, Montreal, Canada

[11]Department of Pediatrics, University of Calgary , Calgary, Canada

[12]Vancouver Coastal Health Research Institute, Vancouver, Canada

Background/Objectives: The province of British Columbia (BC) in Canada (population ~5 million) implemented a voluntary, school-based HPV vaccine program in 2008 for girls in grade 6 (age: 11-12). As in other jurisdictions with early HPV vaccine adoption, these individuals are now becoming eligible for population-based cervical cancer screening. To monitor participation in screening among vaccinated individuals, our objective was to quantify cervical cancer screening uptake in a cohort of young women who received the HPV vaccine and became eligible for screening between 2013 and 2019 in BC, Canada.

Methods: This analysis was conducted in a cohort of young women from BC participating in the QUadrivalent HPV vaccine Evaluation Study (QUEST), which follows participants who received 2 or 3 doses of the HPV vaccine for up to 10 years post-vaccination. They received frequent newsletters about HPV throughout the study. Participants completed annual questionnaires and were asked to self-report having ever had a Pap test. Eligibility for screening was assessed according to BC guidelines, where women 21 years or older or who had been sexually active for 3 or more years were eligible for screening from 2013 to 2015. Eligibility changed to 25 years or older in 2016 with no additional eligibility criteria based on sexual activity. This descriptive analysis quantifies uptake of screening among eligible participants in BC.

Results: As of January 2021, 3333 of 3543 young women from BC in QUEST had completed at least one questionnaire; median age at first questionnaire: 16 years (range: 13-22). As per BC guidelines, 237 (7%) became eligible for screening between 2013 and 2019; the majority (94%) were eligible based on being sexually active for 3 or more years. Of those eligible for screening, 100 (42%) self-reported having had a Pap test, of whom 74% reported having had their Pap within 1 year of becoming eligible, 18% within 2-3 years, and 8% over 3 years after becoming eligible. Of the remaining 3096 young women not indicated for screening per guidelines, 301 (10%) self-reported receiving a Pap test, of whom the majority (96%) were sexually active. Most will become eligible for screening in BC by 2023.

Conclusions: In this volunteer, engaged cohort of vaccinated individuals, self-reported cervical cancer screening among screen eligible participants was low with less than half of those eligible reporting having been screened. However, to validate these results and monitor participation in cervical cancer screening as all participants become eligible, we will be linking QUEST data to administrative data available from the BC provincial cervical cancer screening program.

Partanen Veli-matti
Finland

Partanen Veli-matti
Finland

#3154

Correcting cervical cancer incidence and mortality in the Nordic countries by reallocation of unspecified uterine cancer cases and deaths.

40 - Public health

Partanen V[1], Heinävaara S[1], Anttila A[1], Hakkarainen J[1,2], Lönnberg S[1]

[1]Finnish Cancer Registry, Helsinki, Finland

[2]Central Finland Central Hospital, Jyväskylä, Finland

Background/Objectives: The incidence of and mortality from cervical cancer is underestimated if the presence of uterine cancers, where the exact topography (site of origin) is not specified, is omitted. In this paper we present the corrected figures on mortality from cervical cancer in the Nordic countries by reallocating unspecified uterine cancer deaths and cases to originate either from corpus uteri or cervix uteri. To further validate the accuracy of reallocation, we also analyzed how well the reallocation captures the changes occurring due to a transition in cause of death coding in Norway that took place in 2005.

Methods: This study uses data available in the NORDCAN database, which contains aggregated cancer data from all the Nordic countries for years 1960-2016. The unspecified uterine cancer cases and deaths were reallocated to either cervix uteri or corpus uteri based on the estimated probability that follows the distribution of cases and deaths with verified topography. The estimated proportion of cases and deaths for both cancers were calculated for each combination of age group, year, and country as a proportion of cases (and deaths respectively) with known topography. Annual age-standardized rates were calculated by direct age-adjustment.

Results: The proportions of unspecified uterine cancers were higher in the mortality data than in incidence data, with mean values for years 1960-2016 ranging between 5.1-26.6% and 0.2-6.8% by country, respectively. In the Nordic countries combined, the reallocation increased the number of cases by 4% and deaths by approximately 20% for both cancers. Finland was the only Nordic country, where the mortality rate did not increase substantially after reallocation.

Conclusions: The reallocation procedure had a significant impact on mortality from cervical cancer for countries where the proportion of cancer deaths coded as uterus, not otherwise specified, is substantial. More effort to validate cause of death data with incidence data from cancer registries is warranted to avoid erroneous conclusions of temporal trends based on uncorrected cancer burden.

Suominen Nelli
Finland

Suominen Nelli
Finland

#3621

PERINATAL HPV TRANSMISSION BETWEEN PARENTS AND THEIR OFFSPRING

03 - Epidemiology and natural history

Suominen N[1], Luukkaala T[2,3], Rintala M[1], Grénman S[1], Syrjänen S[4], Louvanto K[4,5]

[1]Department of Obstetrics and Gynecology, Turku University Hospital, University of Turku, Turku, Finland

[2]Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland

[3]Health Sciences, Faculty of Social Sciences, Tampere University, Tampere, Finland

[4]Department of Oral Pathology and Radiology, University of Turku, Turku, Finland

[5]Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere University, Tampere, Finland

Background/Objectives: The knowledge on the routes of human papillomavirus (HPV) transmission in early childhood are scanty. Vertical transmission can occur from either mother or father although father-to-child HPV transmission is less studied. This study aimed to investigate the perinatal (i.e prenatally or at birth) HPV transmission from mothers and/or fathers to their offspring.

Methods: Altogether, 321 mothers, 134 fathers and their 321 offspring from the Finnish Family HPV study cohort were included to the analyses. Parents' genital and oral brush samples in addition to semen samples were collected for HPV testing at baseline (36 week of pregnancy). Oral, genital and umbilical samples from the newborn in addition to placenta samples were collected immediately after delivery. HPV genotyping was performed with Luminex-based Multimetrix kit (Progen Biotechnik GmbH, Heidelberg, Germany) to identify 24 different low-risk (LR) and high-risk (HR) HPV genotypes. Type-specific HPV risk for the child was calculated for each HPV genotype separately from the mother or the father using univariable logistic regression analysis. Univariable- and multivariable-adjusted multinomial logistic regression analyses were used to determine associations between mother's, father's and child's site and LR- and HR-HPV specific status.

Results: Concordance between mother's and her newborn HPV genotype at any site was statistically significant for HPV genotypes 6, 16, 18, 31 and 56, OR ranged from 3.41 (95% CI 1.80-6.48) with HPV16 to 634 (95% CI 28.5-14087) with HPV31. HPV6 and HPV31 also showed statistically significant father-newborn HPV genotype concordance, OR 4.89 (95% CI 1.09-21.9) and OR 65.0 (95% CI 2.92-1448), respectively. Oral HR-HPV infections of the both parents increased the risk of newborn's oral HR-HPV presence, adjusted OR range from 4.87 to 7.72 (95% CI range from 2.10 to 28.3). Newborn's oral LR-HPV infection was predicted only by the mother's oral LR-HPV and the father's urethral LR-HPV infection (adjusted OR range from 7.12 to 7.93 (95% CI range from 1.12 to 56.1). Mother's genital HR-HPV positivity increased the risk of newborn's genital HR-HPV by 3.3-fold (OR of 3.34, 95% CI 1.35-8.30).

Conclusions: The genotype specific HPV concordance between parents and their infant indicates that vertical HPV transmission occurs from both parents to their offspring already during the perinatal period of life.

Saxena Kunal
United States

Saxena Kunal
United States

#3695

Burden of Cervical Conization in Commercially Insured Young and Mid-Adult Women in the United States

26 - Cervical neoplasia

Saxena K[1], Yande S[2], Sawhney B[3], Chatterjee S[3], Kathe N[3]

[1]Merck , Kenilworth, nj, United states

[2]Department of Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, texas, United states

[3]Complete HEOR Solutions, North wales, pa, United states

Background/Objectives: The Advisory Committee on Immunization Practices (ACIP) recommends catch up Human Papilloma Virus (HPV) vaccinations for women ages 13-26 and shared decision making between health care providers and mid-adult (ages 27-45) patients who may benefit from HPV vaccine. However, providers may be hesitant to recommend vaccinations because of lack of data on HPV burden in the adult population. Our analysis estimates the incidence and health care costs for treating cervical lesions, i.e; cervical intraepithelial neoplasia grades 2, 3, and adenocarcinoma in situ (CIN2+) with loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) among commercially insured women, which if untreated may progress to cervical cancer.

Methods: This retrospective cohort study using IBM MarketScan commercial claims database included women aged 18-45, if they had at least 6 months of continuous enrollment, diagnosed with CIN2+, and treated with one of the conization procedures (CKC or LEEP). The annual incidence of conization was estimated from 2016-2019, stratified by age groups: 18-26 years, and 27-45. Adjusted two-year health care costs post conization were computed using multivariable general linear model (GLM) with a gamma distribution accounting for follow-up time, sociodemographic characteristics, and comorbidities, stratified by the same age groups.

Results: The inclusion criteria were met by 6735 women, mean age 33.9 years (SD=6.2). Annual conization incidence declined each year, starting at 156 procedures/100,000 women-years in 2016 to 143 procedures/100,000 women-years in 2019. Conization incidence was lowest for women ages 18-26 (41/100,000 to 62/100,000 women-years) and highest for women ages 31-35 years (243/100,000 to 269/100,000). The adjusted health care costs were $7,279 and $9,249 in the 18-26 and 27-45 age groups, respectively. The adjusted costs for disease-specific care were $3,609 and $4,557 for women ages 18-26 and 27-45 respectively.

Conclusions: Conization burden was found to be high across all age groups, especially in women aged 31-35 years old. The results from this assessment highlight the importance of catch-up vaccination for adult women to preserve their health and reduce future healthcare costs.

FC07- Epidemiology, natural history and public health 2

Pankakoski Maiju
Finland

Pankakoski Maiju
Finland

#3696

IS ORGANIZED CERVICAL CANCER SCREENING MORE EFFECTIVE THAN OPPORTUNISTIC TESTING? A POPULATION-BASED CASE-CONTROL STUDY

40 - Public health

Pankakoski M[1], Ahti A[1], Tytti S[1], Sirpa H[1]

[1]Finnish Cancer Registry, Helsinki, Finland

Background/Objectives: The aim was to study the effectiveness of cervical screening, both organized and opportunistic, on the risk of cervical cancer.

Methods: We conducted a case-control study with 1600 women with invasive cervical cancer diagnosed in 2010—2019 in Finland. On each case, 10 controls were individually matched on age and hospital district. Data on organized and opportunistic screening for these women were derived from the mass screening registry, the pathology laboratories, and the health insurance reimbursement registers. Cervical cancers were linked from the cancer registry. Conditional logistic regression was used to calculate odds ratios for associations between cervical cancer and screening participation three and five years before cases' diagnosis by mode of testing (organized program, unorganized or both). Models were adjusted for socioeconomic status, education, and mother tongue.

Results: Preliminary results will be presented at the conference.

Conclusions: There seems to be little additional preventive effect of opportunistic screening if a well-organized nationwide screening program is in place.

Vaernesbranden Magdalena R.
Norway

Værnesbranden Magdalena R
Norway

#3590

HUMAN PAPILLOMAVIRUS AT MID-GESTATION AND ADVERSE PREGNANCY OUTCOMES: A PROSPECTIVE COHORT STUDY FROM NORWAY AND SWEDEN

40 - Public health

Værnesbranden M[1,2], Staff A[2,3], Sjøborg K[1], Aaneland H[5], Granum B[6], Haugen G[2,3], Hedlin G[7,8], Hilde K[2,3], Lødrup Carlsen K[2,5], Nordlund B[7,8], Rehbinder E[2,9], Skjerven H[2,5], Sundet B[2], Söderhäll C[7,8], Vettukattil R[2,5], Wiik J[1,4], Jonassen C[6,10]

[1]Østfold Hospital Trust , Sarpsborg, Norway

[2]University of Oslo, Faculty of Medicine, Oslo, Norway

[3]Oslo University Hospital, Division of Obstetrics and Gynaecology, Oslo, Norway

[4]Gothenburg University, Dept. of Obstetrics and Gynecology, Gothenburg, Sweden

[5]Oslo University Hospital, Division of Pediatric and Adolescent Medicine, Oslo, Norway

[6]Norwegian Institute of Public Health, Dept. of Environmental Health, Oslo, Norway

[7]Karolinska University Hospital, Astrid Lindgrens Children's Hospital, Stockholm, Sweden

[8]Karolinska Institutet, Dept. of Women's and Children's Health, Stockholm, Sweden

[9]Oslo University Hospital, Dept. of Dermatology and Venaereology, Olso, Norway

[10]Østfold Hospital Trust, Genetic Unit, Center for Laboratory Medicine , Sarpsborg, Norway

[11]Norwegian University of Life Sciences, Faculty of Chemistry, Biotechnology and Food Science, ås, Norway

Background/Objectives: Human papillomavirus (HPV) is a common genital infection, with the highest prevalence during the reproductive years. The association between high-risk HPV (HR-HPV) infections and premalignant and malignant lesions of the cervix, as well as high HPV prevalence during pregnancy is well established. However, the association between HPV infections and adverse pregnancy outcomes is less studied and with conflicting results. This study aimed to investigate the association between HR-HPV infections at mid-gestation and pregnancy outcomes related to placental dysfunction.

Methods: We included 950 women with first-void urine samples collected at the time of enrollment at gestational age 16-22 weeks from the prospective multicenter cohort study of a general population in Norway and Sweden (PreventADALL study, ClinicalTrials.gov NCT02449850). HPV detection and genotyping were performed using the Seegene Anyplex II HPV28 detection essay. This real-time PCR tests presence of genotypes 12 HR-HPV, 8 probably/possibly HR-HPV, and 8 low-risk HPV (LR-HPV). Sociodemographic and pregnancy outcome data were collected using electronic questionnaires and medical records. Adverse pregnancy outcomes were identified as 1. Hypertensive disease of pregnancy (HDP); 2. Gestational diabetes (GDM); 3. Intrauterine growth restriction (IUGR). HDP outcomes included preeclampsia, gestational hypertension, superimposed preeclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. IUGR was defined as ≤ 10% birth weight percentile. We also constructed a composite variable for placental dysfunction related adverse outcomes (HDP, GDM, IUGR and preterm delivery).

Results: Mean age of the women included was 32 years, median pre-pregnant BMI was 25 kg/m2. Prevalence of HR-HPV at mid-gestation was 231/950 (24%). The prevalence of HDP, GDM, IUGR and composite outcome variable was 83/950 (9%), 40/950 (4%), 67/950 (7%) and 168/950 (18%), respectively. We found no association between HR-HPV infections and any of these outcomes, HDP; (OR 1.10, 95% CI 0.64-1.86), GDM; (OR 1.30, 95% CI 0.59-2.86), IUGR (OR 1.70, 95% CI 0.88-3.30), or the composite outcome variable (OR 1.08, 95% CI 0.73-1.60).

Conclusions: In this general population cohort with low prevalence of adverse pregnancy outcomes, but high HR-HPV prevalence, we found no association between HR-HPV infections at mid-gestation and placental dysfunction related adverse pregnancy outcomes at delivery.

Siegenbeek Van Heukelom Matthijs
Netherlands

Schim Van Der Loeff Maarten F.
Netherlands

#3559

HPV TYPE SPECIFIC E6, E7 ANTIBODIES IN HIV-POSITIVE MSM WITH ANAL SQUAMOUS CELL CARCINOMA UP TO 20 YEARS PRECEDING DIAGNOSIS: A CASE-CONTROL STUDY

20 - Serology

Siegenbeek Van Heukelom M[1], Jongen V[2], Waterboer T[3], Van Der Zee R[4], Quint K[5], Prins J[6], Schim Van Der Loeff M[6]

[1]Amsterdam UMC, Amsterdam, Netherlands
[2]Public Health Service Amsterdam, Amsterdam, Netherlands
[3]German Cancer Research Centre, Heidelberg, Germany
[4]Amsterdam UMC, Pathology, Amsterdam, Netherlands
[5]Leiden University Medical Centre, Dermatology, Leiden, Netherlands
[6]Amsterdam UMC, Internal Medicine, Amsterdam, Netherlands

Background/Objectives: Anal human papillomavirus (HPV) infection may lead to anal squamous cell carcinoma (aSCC). aSCC is rare, but is much more common among HIV-positive men-who-have-sex-with-men (MSM). Earlier studies have shown that a substantial proportion of oropharyngeal squamous cell cancer and aSCC cases are seropositive for early antigen 6 (E6) of HPV-16, often years prior to diagnosis. In HIV+ MSM, aSCC is frequently caused by other HPV-types than HPV16. We aimed to assess whether aSCC cases were more often seropositive for E6 and E7 of the causative HPV-type than people living with HIV (PLWH) without aSCC.

Methods: Eligible for inclusion were HIV-positive MSM diagnosed with aSCC, of whom stored serum samples were available at the date of diagnosis and at least one year prior to diagnosis. Serum samples from each calendar year up to 20 years prior to diagnosis were selected for testing. We selected controls (3:1 ratio) among PLWH without aSCC diagnosis, of whom at least 2 stored serum samples were available 10 years apart. All samples were tested for antibodies against E6 and E7 of 10 HPV-types (6,11,16,18,31,33,35,45,52,58). We identified the causative HPV-type for each aSCC by Laser Capture Microdissection of Formalin-Fixed Paraffin-Embedded specimens using SPF10-PCR/LiPA 25. We assessed the association of aSCC with E6/E7 seropositivity using logistic regression. We also analysed time of seroconversion in both cases and controls.

Results: We included 20 cases with aSCC, of which 11 were caused by HPV-16 (55%), two by HPV-18 (10%), two by HPV-52 (10%) and five by other types (25%). Two of 11 HPV-16 aSCC cases (18%) were ever seropositive for E6 and one for E7 (9%); no other cause-specific E6 and/or E7 seropositivity among cases was found. Seropositivity for E6 among the 60 controls varied from n=0 (HPV-6,18,33,52) to n=2 (HPV-16,31,45) (0-3%), and for E7 between n=0 (HPV-18,35,45) and n=1, except for HPV-31 (n=6). The Odds Ratio (OR) for E6 seropositivity detected at least once among cases compared to controls was 8.0 (95%CI 1.6-39.6); for E7 this was 2.4 (95%CI 0.5-10.9). ORs for seropositivity at time of diagnosis were 9.8 (95%CI 1.9-49.0) for E6, and 2.7 (95%CI 0.6-12.6) for E7. The two E6 seropositive HPV-16 cases seroconverted 2-5 years prior to diagnosis; the E7-seropositve HPV-16 case seroconverted 6 years prior to aSCC diagnosis.

Conclusions: HPV-type-specific E6 and E7 seropositivity prior to aSCC diagnosis in HIV-positive MSM was rare and lower than in other studies, but E6 seropositivity was significantly associated with aSCC. Seroconversion to E6 seropositivity occurred 2-5 years prior to diagnosis.

Wendland Eliana Marcia
Brazil

Wendland Eliana Márcia
Brazil

#3698

PREVALENCE OF ANAL HPV INFECTION AMONG UNVACCINATED MEN WHO HAVE SEX WITH MEN IN BRAZIL: PRELIMINARY DATA

28 - Anal neoplasia

Kops N[1], Bessel M[1], Miranda G[1], De Brito E[1], Dall'aqua C[1], Camargo T[1], Da Silva I[1], Comerlato J[1], Dall Soto M[1], Fernandes B[1], Pilz C[1], Fetzner T[1], De Souza F[2], Pereira G[2], Wendland E[1,3]

[1]Hospital Moinhos de Vento, Porto alegre, Brazil

[2]Ministry of Health, Department of STIs, AIDS and Viral Hepatitis, Brasília, Brazil

[3]Universidade Federal de Ciências da Saúde de Porto Alegre, Porto alegre, Brazil

Background/Objectives: Persistent anal human papillomavirus (HPV) infection is the major cause of anal cancer. Despite being rare in the general population, its incidence is elevated in men who have sex with men (MSM). Therefore, we aimed to evaluate the prevalence of anal HPV among unvaccinated MSM in Brazil.

Methods: Cross-sectional study using respondent-driven sampling in 10 capitals cities across all geographical regions. The targeted sample size was initiated with three seeds in each city. For the anal sample, the participants were instructed to insert a Dacron humid swab 3 cm into the anal canal and rotate it 360 degrees at least twice. All samples were processed in a certified central laboratory using Anyplex II HPV 28 detection (Seegene®).

Results: A total of 628 unvaccinated MSM were recruited. Most were single (65.55%), with a mean age of 29.73 + 9.42 years, 44.83% white skin color and with university education (77.73%). The overall HPV prevalence was 74.68% (n = 469), being 16.24% for HPV type 16 and 6.53% for HPV type 18.

Conclusions: Thesepreliminary data show a high prevalence of HPV in the unvaccinated MSM Brazilian population. Further studies are warranted on the impact of HPV vaccination on anal cancer in this specific population.

Kusters Johannes
Netherlands

Kusters Johannes
Netherlands

#3523

TYPE-SPECIFIC CONCORDANCE OF HPV INFECTION BETWEEN THE GENITAL AND ANAL SITES FOR YOUNG WOMEN AND MSM

03 - Epidemiology and natural history

[1]National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands
[2]Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands

Background/Objectives: Concordant human papillomavirus (HPV) infection between genital and anal sites is common among women, and may be common among men who have sex with men (MSM). It is unclear what the risk factors are for type-specific anogenital concordance, but two potential risk factors could be receptive anal intercourse (RAI) and autoinoculation. Therefore, this study aimed to investigate the occurrence of type-specific anogenital concordance among young women and MSM visiting sexual health clinics in the Netherlands, and to identify risk factors for type-specific anogenital concordance.

Methods: Data from the PASSYON study, a biennial repeated cross-sectional study in the Netherlands, between 2009 and 2019 were used. Genital and anal HPV infections were identified for 25 HPV genotypes (SPF10-LiPA25). Cohen's kappa was used to assess the degree of type-specific concordance. Provided that at least moderate concordance (κ>0.4) was found, risk factors for type-specific concordance were identified using logistic regression with generalised estimated equations. In this model, genital-only infections were compared to type-specific concordant infections. Receptive anal intercourse (RAI) was forced into the multivariable model to investigate its impact on concordance. All analyses were done for women and MSM separately.

Results: The study population consisted of 1,492 women and 614 MSM. Among women,type-specific anogenital concordance was common; 607 women (40.7%) had at least one type-specific concordant infection, and kappa was above 0.4 for 20 genotypes. Anogenital concordance was found most often for HPV-51 (10.7%); the highest kappa was found for HPV-6 (κ = 0.60). Among MSM type-specific anogenital concordance was not common; 64 men (10.4%) had at least one concordant infection, and kappa was inf0.4 for all genotypes. Risk factors were determined for concordance among women. The multivariable model was based on 2,677 genital infections (genital-only: n=1,622; concordant: n=1,055), and the only significant risk factor for type-specific concordance among women was genital chlamydia (adjusted OR 1.5, 95%CI: 1.2 - 1.9). RAI was not associated with concordant infection (OR 1.1, 95% CI: 0.9 - 1.3).

Conclusions: Type-specific concordant HPV infection between the genital and anal sites was common among young women, and uncommon among MSM.The only significantly associated risk factor for concordance among women was genital chlamydia infection. As no other observed sexual or demographic risk factor was associated, autoinoculation seems a likely explanation for concordant HPV infection between genital and anal sites for women.

Smith Jennifer
United States

Smith Jennifer
United States

#3918

EXTENDED HUMAN PAPILLOMAVIRUS GENOTYPING TO PREDICT PROGRESSION TO HIGH-GRADE CERVICAL PRECANCER: A PROSPECTIVE COHORT STUDY IN THE SOUTHEASTERN UNITED STATES

03 - Epidemiology and natural history

Smith J[1,9], Bukowski A[1], Hoyo C[2], Hudgens M[3], Brewster W[1,4], Valea F[5], Bentley R[6], Vidal A[7], Maguire R[2,8], Schmitt J[8], Murphy S[8], North K[1]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel hill, United states
[2]Department of Biological Sciences, Center for Human Health and the Environment, North Carolina State University, Raleigh, United states
[3]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel hill, United states
[4]Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel hill, United states
[5]Department of Obstetrics and Gynecology, Virginia Tech Carilion School of Medicine, Roanoke, United states
[6]Department of Pathology, Duke University School of Medicine, Durham, United states
[7]Department of Surgery, Cedars-Sinai Medical Center, Los angeles, United states
[8]Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, United states
[9]Lineberger Comprehensive Cancer Center, Chapel hill, United states

Background/Objectives: High-risk human papillomavirus (hrHPV) testing is recommended for primary cervical cancer screening and is used alongside cytology to triage screening abnormalities to colposcopy. Most screening-based hrHPV tests involve pooled detection of any hrHPV type or of HPV 16/18 only. Extended HPV genotyping, particularly of non-16/18 hrHPV types, may improve risk stratification for millions of cervical abnormalities detected each year, but HPV genotype-specific progression risks are not well characterized. HPV genotype-specific incidence of high-grade cervical intraepithelial neoplasia or more severe (CIN2+) was examined among individuals with normal or low-grade (CIN1) histology following an abnormal screening cytology result.

Methods: A US-based prospective, multiracial cohort of 343 colposcopy referral patients with normal (n=226) or CIN1 (n=117) histology was assessed. Baseline cervical samples underwent HPV DNA genotyping. Participants were followed for up to five years. Genotype-specific CIN2+ incidence rates (IR) were estimated with accelerated failure time models for interval-censored data. Cumulative CIN2+ risk over five years was estimated non-parametrically and compared for HPV risk groups (HPV 16/31/18, else HPV 33/58/52/45, else HPV 39/68/35/51/59/56/66) and age groups (ages 21-24, 25-29, 30+).

Results: At enrollment, median participant age was 30.1 years; 67.1% were hrHPV-positive. During follow-up (median 24.3 months), 24 participants progressed to CIN2+ (7.0%; 6.2% among normal histology and 8.6% among CIN1). CIN2+ IR among hrHPV-positive participants was 3.2/1,000 person-months. CIN2+ IRs were highest for HPV 16 (IR 8.3; 95% CI 4.1, 16.6), HPV 33 (IR 7.8; 95% CI 2.0, 31.3), and HPV 58 (IR 4.9; 95% CI 1.2, 19.6). IRs were highest for HPV 16, 68, and 33 among normal histology and for HPV 33, 31, 16, and 58 among CIN1. Five-year CIN2+ risks were 0.27 for HPV 16/31/18, 0.11 for HPV 33/58/52/45, and 0.13 for HPV 39/68/35/51/59/56/66 (p=0.04). CIN2+ risk did not differ by age group.

Conclusions: In addition to the established HPV type 16, HPV 33 and 58 were consistently predictive of progression to CIN2+ over a five-year period in this cohort. These findings also support the utility of HPV risk groups to stratify women with non-16/18 hrHPV positivity who exhibit differential risks of progression. Additionally, HPV risk groups appear to predict progression regardless of age; thus, although hrHPV testing is not recommended for initial screening of women under 30 years of age, it may be a risk-stratification tool for these younger women, once a cervical abnormality is found. In conclusion, extended genotyping of non-16/18 hrHPV may be useful to identify individuals with normal or low-grade histology results who are at increased risk of progression to CIN2+, thereby improving the efficacy of cervical cancer screening.

Rasmussen Christina Louise
Denmark

Rasmussen Christina Louise
Denmark

#3701

INFLUENCE OF HPV AND P16 EXPRESSION ON SURVIVAL AFTER VULVAR SQUAMOUS CELL CARCINOMA: A POPULATION-BASED DANISH STUDY OF ~1,300 CANCERS

27 - Vulvar diseases and neoplasia

Rasmussen C[1], Thomsen L[1], Baandrup L[1,2], Frederiksen K[3], Franzmann M[4], Larsen L[5], Mejlgaard E[6], Schledermann D[7], Villena N[8], Waldstrøm M[9,10], Winberg B[2], Oernskov D[9], Kjaer S[1,11]

[1]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
[2]Department of Pathology, Herlev Hospital, Herlev, Denmark
[3]Unit of Statistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark
[4]Department of Pathology, Hvidovre University Hospital, Hvidovre, Denmark
[5]Department of Pathology, Zealand University Hospital, Naestved, Denmark
[6]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark
[7]Department of Pathology, Odense University Hospital, Odense, Denmark
[8]Department of Pathology, Aalborg University Hospital, Aalborg, Denmark
[9]Department of Pathology, Vejle Hospital, Lillebaelt Hospital, , Vejle, Denmark
[10]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark
[11]Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background/Objectives: Some studies have shown that human papillomavirus (HPV) status may be a prognostic marker for survival after vulvar cancer, alone or in combination with p16 expression. However, the previous studies were small and had heterogeneous findings. In this large, nationwide study, we estimated survival after vulvar squamous cell carcinoma (SCC) according to high-risk (hr) HPV status, alone and combined with p16 expression.

Methods: In a nationwide pathology register, we identified all cases of vulvar SCC diagnosed at 13 pathology departments in Denmark during 1990-2017 (n=1545). Archived formalin-fixed, paraffin-embedded tumor tissue blocks were retrieved from clinical biobanks, and diagnoses were reviewed by a gynecopathologist. At a central laboratory, all samples were tested for HPV with the INNO LiPA Genotyping Extra test, and CINtec histology staining for p16 was performed. All p16 slides were evaluated by two gynecopathologists independently, and tumors with >70% p16 staining cells were considered positive. From nationwide registries, we obtained information on emigration and deaths in the study population during up to 28 years of follow-up. We estimated the 5-year overall survival (OS) according to hrHPV and p16 status by Kaplan-Meier's method, and the hazard ratio (HR) of 5-year mortality was estimated by Cox regression, adjusting for age and year of diagnosis.

Results: Of the originally identified 1545 vulvar SCCs, we included 1278 cases (83%) for whom an archived tissue block could be located, the diagnosis was verified and we had valid HPV and p16 results. The median age at diagnosis was 72 years (range 27-102). The majority of cases were histologically classified as SCC, not otherwise specified (67.0%), followed by keratinizing SCC (23.3%). The prevalence of hrHPV was 52.0% (95% CI: 49.1-54.6), and 31.0% (95% CI: 28.4-33.5) of cases were positive for both hrHPV and p16. hrHPV positive women had better survival than hrHPV negative women (5-year OS: 61.0% versus 43.9%; HR 0.82, 95% CI, 0.66-0.98). Furthermore, women positive for both hrHPV and p16 expression had better survival than women who were negative for both markers (5-year OS: 69.7% versus 43.9%, HR 0.67, 95% CI, 0.45-0.89).

Conclusions: These preliminary analyses support that patients with hrHPV positive vulvar SCC have improved overall survival compared with hrHPV negative patients. Combined positivity for HPV and p16 expression appears to be a stronger prognostic marker than positivity for HPV alone. Further analyses will be presented at the conference, including estimates of disease-specific survival and analyses adjusted for other prognostic factors, including tumor stage.

Boero Veronica
Italy
Boero Veronica
Italy

#3376

The "CIV Classification," a New Proposal for the Architectural Grading of Vulvar Lichen Sclerosus

27 - Vulvar diseases and neoplasia

[1]Gynecology Unit, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy
[2]Department of Gynecology, "Humanitas San Pio X," , Milan, Italy
[3]Plastic Surgery Service, Gynecology Unit, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy
[4]Department of Gynaecologic Oncology, Nuffield Department of Women's and Reproductive Health (WRH), University of Oxford, Oxford, United kingdom
[5]Lower Genital Tract Disease Unit, Obstetrics and Gynecology Department, Ospedale Vittore Buzzi, Milan, Italy

Background/Objectives: The purpose of this cross-sectional study was to prepare a reliable and easy-to-use architectural classification for vulvar lichen sclerosus (VLS) aimed at defining the morphological patterns of this condition.

Methods: An expert panel composed by 7 physicians with expertise in clinical care of vulvar conditions outlined the architectural criteria for the definition of VLS severity (phimosis of the clitoris, involvement of the interlabial sulci, narrowing of the vulvar introitus), identifying 5 grades to build up a classification. Thirteen physicians with 2-30 years expertise in vulvar diseases (nonexpert group) were asked to evaluate 3-5 pictures from 137 patients. Each physician individually assigned a grade to each case, according to the previously mentioned criteria. Interrater reliability was analyzed by means of intraclass correlation coefficient (ICC). The reliability concerning the 2 classifications of each rater was analyzed by means of κ statistic. Intraobserver and interobserver reliability in vivo was analyzed by means of κ index.

Results: This study provides a new classification of VLS, based on defined anatomical criteria and graded into mutually exclusive progressive classes.The ICC analysis showed a substantial interrater reliability of the classification, ICC = 0.89 (0.87-0.91), both in the expert panel and in the nonexpert group (ICC = 0.92 and 0.87, respectively). An "almost perfect" intraobserver and interobserver reliability was achieved among physicians in vivo (κ = 0.93).

Conclusions: Our classification showed a high reliability. It is easy to use, and it can be applied in clinical practice and eventually, in the evaluation of regenerative and cosmetic surgery.

Wiik Johanna
Norway

Wiik Johanna
Sweden

#3723

MATERNAL HUMAN PAPILLOMAVIRUS INFECTION DURING PREGNANCY AND PRETERM DELIVERY, A MOTHER-CHILD COHORT STUDY IN NORWAY AND SWEDEN

03 - Epidemiology and natural history

Wiik J[1,2], Værnesbranden M[1,4], Jonassen C[5,6], Staff A[4,8], Lødrup Carlsen K[4,9], Hilde K[4,8], Sundet B[4], Skjerven H[4,9], Rehbinder E[4,10], Nordlund B[11,12], Vettukttil R[4,9], Granum B[5], Haguen G[4,8], Hedlin G[11,12], Söderhäll C[11,12], Jacobsson B[2,13], Nilsson S[14,15], Sengpiel V[2,3], Sjøborg K[1]

[1]Department of Gynecology and Obstetrics, Østfold Hospital Trust,, Kalnes, Norway

[2]Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Region Västra Götaland, Sahlgrenska University Hospital, Department of Obstetrics and Gynecology, Gothenburg, Sweden

[4]University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Oslo, Norway

[5]Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

[6]Genetic Unit, Centre for Laboratory Medicine, Østfold Hospital Trust,, Kalnes, Norway

[7]Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, , ås, Norway

[8]Division of Obstetrics and Gynaecology, Oslo University Hospital, , Oslo, Norway

[9]Division of Pediatric and Adolescent Medicine, Oslo University Hospital, , Oslo, Norway

[10]Department of Dermatology and Venereology, Oslo University Hospital, Oslo, Norway

[11]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

[12]Department of Women´s and Children´s Health, Karolinska Institutet, , Stockholm, Sweden

[13]Department of Genetics and Bioinformatics, Division of Health Data and Digitalisation, Institute of Public Health,, Oslo, Sweden

[14]Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg,, Gothenburg , Sweden

[15]Department of Mathematical Sciences, Chalmers University of Technology,, Gothenburg, Sweden

Background/Objectives: Human papillomavirus (HPV) is a common infection in reproductive age. Infection, inflammation and placental dysfunctuon are leading causes for preterm delivery. This study aimed to assess the association between HPV infection in pregnancy and preterm delivery (PTD), prelabour rupture of membranes (PROM), preterm prelabour rupture of membranes (pPROM), chorioamnionitis and neonatal sepsis.

Methods: Pregnant women participating in a prospective multicenter cohort study of a general population in Norway and Sweden (PreventADALL, ClinicalTrials.gov, NCT02449850) provided samples for HPV-DNA detection in first void urine at mid-gestation and at delivery, and from placenta after delivery. The association between HPV-DNA presence; any HPV (28 genotypes), any high risk HPV (12 HR-HPV) or HPV 16 and PTD, pPROM, PROM, chorioamnionitis and neonatal sepsis was analyzed using logistic regression adjusted for relevant confounders. In women positive for HR-HPV at mid-gestation, we examined if persistence of HPV, viral load or presence of multiple HPV infection were associated with obstetric outcomes.

Results: The study included 950 women (mean age 32 years) with singelton pregnancies and valid urine HPV test at mid-gestation and obstetric outcomes, whereof 753 also had a valid urine HPV test at delivery. At mid-gestation, 24% were positive for any HR-HPV and 40% for any HPV. The frequency of PTD was higher in HR-HPV positive (3.5%) than in HR-HPV negative women (2.1%) at mid-gestation but the association was non-significant (addjusted odds ratio 1.71 (95% CI 0.70-4.19), p=0.24. We found no significant association between presence or persistence of HR-HPV or HPV at mid-gestation or delivery and PTD, pPROM, PROM, chorioamnionitis or neonatal sepsis. HPV-DNA was not detected in any of the placentas in women with PTD, pPROM or chorioamnionitis.

Conclusions: HPV infection during pregnancy was not assoociated with PTD, pPROM, PROM, chorioamnionitis or neonatal sepsis in this general population with a low incidence of adverse obstetric outcomes.

FC10 - Diagnostic procedures and management

Mesquita Pinto Ana Rita
Portugal

Sousa Rita
Portugal

#3784

LASER VAPORIZATION FOR TREATMENT OF LOW-GRADE CERVICAL LESIONS: A SINGLE CENTRE STUDY

25 - Colposcopy

Mesquita Pinto R[1], Silva S[2], Carvalho C[3], Raposo S[4], Sousa R[4]

[1]Centro Hospitalar Tondela-Viseu, Viseu, Portugal

[2]Unidade Local de Saúde Alto Minho, Hospital Santa Luzia, Viana do Castelo, Viana do castelo, Portugal

[3]Maternidade Dr. Alfredo da Costa – Centro Hospitalar de Lisboa Central, EPE, Lisboa, Portugal

[4]Instituto Português de Oncologia de Coimbra, Coimbra, Portugal

Background/Objectives: Low grade intraepithelial lesions (LSIL) of the cervix are histological manifestations of HPV infection, with a very high regression rate, specially in young women. Management of this patients is an issue of debate, being an option for persistent lesions preceded by minor findings, destructive treatments. The aim of this study was to evaluate the success of laser vaporization for low grade cervical lesions.

Methods: Retrospective study of the 104 women with biopsy-proven CIN1 who underwent laser vaporization between January and December 2020 in Instituto Português de Oncologia de Coimbra, Portugal. The regression and persistence of the lesion were evaluated.

Results: Most of them, 54 (52%) women returned to the regular screening program. Thirty eight (36,5%) women remained in the colposcopy clinic for follow-up, with one case of excisional treatment, due to long-term lesion persistence, after two vaporizations. Twelve of the patients missed the follow-up appointment (11,5%). Eleven patiens were vaccinated and 23% smokers.

Conclusions: Most of low grade cervical lesions were successfully treated with laser vaporization (52%), presenting a negative HPV test at 6 months-follow-up. The need of a posterior excisional procedure was of one case (< 1%). CO2 laser vaporization, a simple procedure, performed in outpatient clinics, may be a successful option for low grade cervical lesions.

Gori Silvia
Italy
Gori Silvia
Italy

#3614

CONSERVATIVE MANAGEMENT OF WOMEN WITH CIN2 LESIONS ENROLLED IN A PROSPECTIVE MULTICENTRIC STUDY: AGE PREVALENCE AND APPLICABILITY.

23 - Diagnostic procedures / management

Gori S[1], Frayle H[1], Pagan A[2], Solda' M[3], Romagnolo C[3], Insacco E[4], Laurino L[3], Matteucci M[4], Sordi G[5], Busato E[2], Zorzi M[6], Maggino T[3], Del Mistro A[1], Cin2 Study Working Group .[1]

[1]Veneto Institute of Oncology IOV-IRCCS, Padova, Italy
[2]Local Health Unit Marca Trevigiana, Treviso, Italy
[3]Local Health Unit Serenissima, Venezia, Italy
[4]Azienda Ospedale Università, Padova, Italy
[5]Local Health Unit Scaligera, Verona, Italy
[6]Veneto Tumour Registry, Azienda Zero, Padova, Italy

Background/Objectives: The detection and treatment of high-grade cervical lesions prevent the development of invasive cervical cancer. Excisional procedures can pose a risk for subsequent pregnancies, thus conservative management of Cervical Intraepithelial Neoplasia grade 2 (CIN2) lesions should be adopted in young women. We are conducting a prospective multicentre study aimed to evaluate feasibility and efficacy of CIN2 conservative management, as well as the role of different biomarkers. Here we analyse women's eligibility and acceptance.

Methods: Data on all women diagnosed with CIN2 between April 2019 and October 2021 in four centres within organised screening in the Veneto region were collected. Women fitting the study's predefined criteria and willing to participate were recruited. Inclusion criteria were: age 25-45 yrs, transformation zone and lesion fully visible at colposcopy. Exclusion criteria were: pregnancy, previous treatment of a CIN2+ lesion, immunodeficiency, and presence of an endocervical lesion not completely visible at colposcopy. Women are grouped as: not eligible; eligible but refused participation; enrolled. Women are followed for 24 months, with colposcopy and testing for several biomarkers. Upon signing an informed consent, women are enrolled in the study and cervical cell samples collected. Treatment is delayed and subsequently performed in the case of lesion progression, or persistence for >12 months.

Results: Overall, 640 women were diagnosed with CIN2; 228 (35,6%) not eligible; 93 (22,6%) eligible but refused; 319 (77,4%) enrolled. The most frequent reason of exclusion was age >45 yrs. Among eligible not enrolled women, refusal/willingness to be treated accounted for 78,5%. CIN2 prevalence, no eligibility, eligibility, refusal and acceptance rates by age (expressed as number and %) are reported in Table 1.

Conclusions: The distribution of CIN2 lesions by age in our area indicates slightly higher figures before 40 years of age. According to the inclusion/exclusion criteria set for our study, we could enrol half of the cases diagnosed. Acceptance was (not significantly) higher among 25-34-yrs-old than among older women. At the completion of the study, the clinical outcome and the results of the biomarkers could envisage more effective criteria.

Table 1

Siegler Efraim
Israel

Siegler Efraim
Israel

#3626

Clearance of High-Risk HPV after Large Loop Excision of Transformation Zone of Early Stage Cervical Cancer and Adenocarcinoma in Situ has a high correlation with absence of residual disease

26 - Cervical neoplasia

Siegler E[1], Goldberg Y[1,2], Siegler Y[3], Mazarebe S[5], Kugelman N[1], Sabu E[2,5], Lavie O[1,2], Shaked-mishan P[4], Mackuli L[1], Segev Y[1,2]

[1]Department of Obstetrics , Haifa, Israel

[2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, , Haifa, Israel

[3]. Department of Obstetrics , Haifa, Israel

[4]Clinical Serology and Virology Laboratory, Carmel Medical Center, Haifa, Israel

[5]Department of Pathology, Carmel Medical Center, Haifa, Israel

Background/Objectives: Better predictors of recurrence are needed after fertility preserving surgery in women with early-stage cervical cancer and adenocarcinoma in situ (AIS).We assessed a possible correlation of High-Risk human papillomavirus (HR-HPV) clearence after large loop excision of the transformation zone (LLETZ) in women diagnosed with early-stage cervical cancer and AIS with no residual cancer .

Methods: Data were collected from 102 women diagnosed with early-stage invasive cervical cancer and AIS , who HR-HPV positive and had a repeat cervical HPV test short time after the operation, 3-12 weeks post LLETZ , and before the final surgical treatment.We compared characteristics of women with negative and positive HR-HPV post LLETZ

Results: At the post -LLETZ follow up visit , 45 women were negative and 57 wer HR-HPV positive for HR=HPV.The pathological results of women who were HR-HPV negative compared to HR-HPV positive after LLETZ included a significantky higher incidence of adenocarcinoma and AIS : 21 (46.7%0 vs 8(14%) , (p=0.0005): higher proportion with early stage cervical cancer.In the negative Hr-HPV after LLETZ 40(88%) women had normal histology and only 2(4.4%) had cancer in the final histological specimen. Among women who underwent radical hysterectomy/trachelectomy after LLETZ , a normal final histology was observed in 75% (9/12) of HR-HPV negative and 8.7% (2/23) of HR-HPV positive ($p<0.0001$) . The negative predicted value of negative Hr-HPV after LLETZ was 95.6%

Conclusions: Clearence of HR-HPV from the cervix a short perion after LLETZ has ahigh correlation wuth absence of residual cancer in the outcome , either in the final pathology or the follow up.Testing for HR-HPV a short period after LLETZ might serve as a new parameter for risk assesment : a negative HR-HPV result may suggest the need for a less radical operation in women with early-stage cervical cancer.

Jeremic Igor
Serbia

Igor Jeremic

#3065

The sync up of colposcopic findings with cervix precancerouses changes in cervix with young female patients

25 - Colposcopy

Igor J[1]

[1]Clinic Jeremic, Belgrade, Serbia

Background/Objectives: The study included 120 young female patients age 17-30 from Serbia, Montenegro Bosnia and Hercegovina as well as patients from EU countries. All patients had HPV confirmed diagnosis (DNK type procedure). Predominant types with patients in Serbia were 6,31,33,45,52,56,66 Montenegro: 16,18,44, 35, 33, 51,56,62,68 whereas the patients from Bosnia and Herzegovina and EU countries had a combination of the afore stated ones. The organism of young females is unprepared and the incubation period is shortened from 3 weeks to 3 months.

Methods: A colposcopy procedure has been done to all patients. Depending on the severity of HPV infection, colposcopy findings differed. With younger patients (17-21 years of age) more severe infection resulted in a combination of several pathological images (mosaic, punctation Aw epithelia) whereas with older patients (25-30 years of age) we found out often leuco-plaque and irregular vascular pattern. With these patients we performed the removal of the changes by application of radio wave LOOP excision. The essence of the technique is the combination of radio wave excision and deep vaporization. With excision we remove the change in the width of up to 3, 5 cm and depth of 2,5 cm, and with additional deep vaporization of the bottom of the change we remove displastic change, all in local anesthesia in 3 to 5 minutes.

Results: Each female patient had a confirmed diagnosis of HPV infection of the cervix. With 47% H-SIL has been diagnosed, and 21% of patients had HPV cervicitis condylomtosa. The majority of patients with H-SIL diagnosis were younger than 25 years and after colposcopy procedure the findings were a mixture of pathological images, which appeared immediately upon smearing of the cervix with dilution of vinegar acid (AW epithelia, rough mosaic, and punctuation in the majority of cases). L-SIL was dominant with colposcopy image of rough AW epithelia or mosaic.

Conclusions: Pathological colposcopic findings is a clear indicator of HPV infection of the cervix. In case there is a combination of a number of pathological images, it is necessary to apply an adequate therapeutical procedure in accordance with the patient's age. It is very important to note that combination of HPV viruses at this particular gegraphical location is entirely present in polyvalent HPV vaccines.

References: . Patented the special technique of radiowave LOOP excision with radiowave vaporization as a method of treatment of choice with difficult cases of dysplasia on PVU (CIN I,CIN II, CIN III) 5. Patented the special technique of removal of condyloms on vagina and mucous membrane of labia (radiowave vaporization) 6. Patented the technique of removal of giant anal and intraanal condyloma, with the use of the mixed technique of radiowave vaporization and excision, without bleeding. 20 years of work only in the field of HPV infections More than 6000 edited RF LOOP excisions.

HPV -RF therapy

GÅ?Ä„b Grzegorz
Poland

Glab Grzegorz
Poland

#3549

Clinical evaluation of the Mobile ODT AVE (AI) application VisualCheck 1.5 versus 2.0: comparison with human colposcopic assessment

22 - Artificial Intelligence

[1]Grzegorz Głąb, Opole, Poland
[2]Aleksandra Zimmer-Stelmach, WrocŁaw, Poland
[3]Jan Żak, WrocŁaw, Poland

Background/Objectives: The use of artificial intelligence (AI) algorithms to analyze images of the cervix made with the EVA System Mobile ODT device creates new possibilities in the diagnosis of precancerous and cervical cancer in everyday practice. It can be used wherever a gynecological examination with cervical visualization can be performed and where there is access to Internet networks. Indeed, the system can be used not only by doctors skilled in colposcopy, but also by trained medical personnel with much less experience. The use of VisualCheck® (Mobile ODT, Tel Aviv) application allows for remote online "consultation" of captured images of the cervix after the application of 3-5% acetic acid. The algorithm result, based on hundreds of thousands of images collected in a cloud-based database has been compared to the assessments of experienced colposcopists, and correlation has been shown to be verified. The obtained result allows for the initial identification of the examined women as owners of physiological changes (not suspected to be cancerous) and those with suspected lesions, for whom further in-depth diagnosis is advised (colposcopy after biopsy, HPV HR DNA genotyping, CINTec, or LBC).

Methods: The aim of the study was to compare the diagnostic performance parameters of two versions of the VisualCheck 1.5 application from 2020 and the next, improved version of VisualCheck 2.0 from 2021. The algorithm result for both versions of randomized images from daily practice was compared to assessment of experienced colposcopists. All women identifficated by AI as suspected and false negative by colposcopist were verified by histopathologic biopsy and PCR DNA HPV HR 14 type genotyping The sensitivity, diagnostic specificity and the value of Youden's index were calculated for two groups of patients similar in size.

Results: Results: In 2020, 204 results of the study evaluated by the VisualCheck 1.5 versions were assessed, achieving a sensitivity of 89,6%, specificity of 69,2% and a Youden ratio of 58,9%. In 2021 another 269 results of the analysis were analyzed by the modified version of the VisualCheck 2.0 application, obtaining a sensitivity of 92,2%, specificity of 79,4% and the value of Youden index of 77%.

Conclusions: - Both the VisualCheck 1.5 and 2.0 applications have a high diagnostic sensitivity of approx. 90%, which allows the method to be used as an effective primary screening tool. - The VisualCeck 2.0 application has a specificity, which significantly reduces the numbers of false positives compared to version 1.5. The increase in the value of the Youden's index from 58,9% to 77,7% confirms the greater usefulness of 2.0 version as a support for screening tests with the use of EVA System Mobile ODT in everyday practice. - The obtained results confirm the importance of further research on larger populations in other countries, and with biopsy serving as the reference standard in order to further improve and validate AI technology for cervical assessment with the EVA System.

Kalteis Martin Simon
Germany

Kalteis Martin Simon
Germany

#3506

ESTABLISHMENT AND OPTIMIZATION OF A SOFTWARE-BASED 3D RECONSTRUCTION WORKFLOW FOR ORGANOTYPIC CULTURE MODELS

21 - New technologies

Kalteis M[1,2], Altmann J[1,2], Köhler R[1,2], Stark H[1,2], Von Knebel Doeberitz M[1,2], Prigge E[1,2]

[1]Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

[2]Clinical Cooperation Unit F210, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background/Objectives: Three-dimensional (3D) in vitro model systems are increasingly used to study the effects of pharmacological substances in environments that aim to represent in vivo conditions more accurately than traditional 2D cell culture. We recently established a 3D organotypic culture (OTC) model mimicking HPV-induced precancerous lesions in order to evaluate the effects of new therapeutic approaches on lesion size and morphology in response to distinct treatment conditions. In order to characterize changes in tissue model architecture, we developed an open-source-software-based workflow that uses digital image stacks of whole-slide-scanned serial tissue sections to generate 3D renderings for visualization and analysis.

Methods: OTCs were formalin-fixed, paraffin-embedded and serially sectioned into 14 µm thick consecutive tissue sections, which were stained with Meyer's Hematoxylin and Eosin and subsequently scanned on a Hamamatsu S210 whole-slide-scanner imaging system. Tumor cell areas were detected by a custom-trained classifier using QuPath [1] and converted into binary masks. Images and masks were registered, stacked and color-deconvoluted in ImageJ [2,3] and finally fused and rendered as 3D volumes using Fluorender [4] . Tumor lesion volume was approximated by multiplying the segmented lesion area per image by the distance between two consecutive layers and summing the results for the complete stack in a script written for QuPath. Generalizability and adaptability were assessed by applying the workflow to generate 3D reconstructions of different tissue types.

Results: Using the newly established tissue processing and analysis workflow, we were able to reconstruct the 3D morphology of tumor lesions in our organotypic culture model. Different segmentation approaches were evaluated in QuPath and a pixel classifier trained on hand annotated data was selected as the best-performing approach in our dataset. Manual registration of image stacks was satisfactory but laborious and is a potential candidate for further automation. Rendered volumes can be viewed and interacted with in real time and export of images and video sequences is possible. Volumetric computation of tumor cell burden could be successfully performed.

Conclusions: We successfully established a workflow based on serial tissue sections and whole-slide-image stacks that enables 3D reconstruction and visualisation of OTC models. It allows for an in-depth study of the spatial configuration and size of HPV-induced lesions during the course of different treatment approaches. Using scriptable open-source software as building blocks makes our workflow cost-effective, flexible and easily adaptable to different tissue types and segmentation targets.

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Lujan Elena
Spain

Gaslain Yann
Spain

#3710

EFFICACY OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HIGH-RISK HPV WOMEN OVER 40: SUB-ANALYSIS OF THE PALOMA CLINICAL TRIAL & PAPILOBS REAL-LIFE STUDY

26 - Cervical neoplasia

Gaslain Y[1], Cortés J[2], De Santiago J[3], Gaslain Y[4]

[1]Instituto Palacios, Salud y Medicina de la Mujer, Madrid, Spain

[2]Private Practice, Palma, Spain

[3]Centro Oncológico MD Anderson, Madrid , Spain

[4]Procare Health Iberia, Barcelona , Spain

Background/Objectives: HPV clearance and resolution of cervical HPV-dependent lesions become difficult in peri and postmenopausal women. The objective of this analysis was to evaluate the effect of the Papilocare®, a multi-ingredient Coriolus versicolor-based vaginal gel in repairing the high-risk (HR) HPV-dependent low-grade cervical lesions in women over 40 years.

Methods: Paloma study (ClinicalTrials.gov NCT04002154) was a multicenter, randomized, open-label, parallel-group, watchful waiting approach-controlled clinical trial. Unvaccinated HPV positive women aged between 30-65 with cytology of ASCUS or LSIL and concordant colposcopy image were randomized into 3 groups: A) Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months; B) Papilocare® 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months; C) Control group: watchful waiting approach. Papilobs study (ClinicalTrial.gov: NCT04199260) was an observational, multicenter, prospective, one-cohort study. Vaccinated or not HPV-positive women aged > 25y with cytology of ASCUS or LSIL and concordant colposcopy were included. Patients were treated with Papilocare® 1 cannula/day for 21 days during first month + 1 cannula/alternate days for 5 months. Percentages of patients with normal cytology and concordant colposcopy after 6 months of treatment in the HR-HPV population are presented.

Results: A total of 30 and 68 HR-HPV patients above 40yo were evaluated in Paloma and Papilobs studies, respectively. In the Paloma trial, normal cytology and concordant colposcopy was observed in 90% vs 33% patients in A+B Papilocare® and control groups, respectively, (p=0.003, Fisher test). In the Papilobs study, normal cytology and concordant colposcopy was achieved in 73,5% of patients.

Conclusions: After a 6-month treatment period,Papilocare® showed a clinically robust and statistically significant efficacy in repairing cervical HR-HPV lesions in women over 40 years vs watchful waiting approach. This efficacy was corroborated in the real-life study in more than 2/3 of the HR-HPV patients above 40.

ASCUS/LSIL cervical lesions normalization

Reuschenbach Miriam
Germany

Luzak Agnes
Germany

#3382

BURDEN OF CONIZATION AND ASSOCIATED HEALTHCARE COSTS IN WOMEN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) - AN ANALYSIS OF GERMAN STATUTORY HEALTH INSURANCE CLAIMS DATA FROM 2013-2018

26 - Cervical neoplasia

[1]Global Medical and Scientific Affairs, MSD Sharp , Munich, Germany
[2]Department of Market Access, MSD Sharp , Munich, Germany
[3]Center for Observational and Real-World Evidence (CORE), Merck , Kenilworth, nj, United states
[4]Xcenda GmbH, Hanover, Germany
[5]Department of Health Economics and Health Care Management, Bielefeld School of Public Health, Bielefeld University, Bielefeld, Germany
[6]Department of Gynecology, University of Düsseldorf, Düsseldorf, Germany

Background/Objectives: Cervical intraepithelial neoplasia (CIN) is caused by human papillomavirus (HPV) infection. Management of CIN includes watchful surveillance or excision by conization. Data on clinical and economic burden of CIN and its treatment are limited for Germany. This study aimed to assess annual conization rates in women aged 18-45 years and related healthcare costs during a two-year follow-up period from the German statutory health insurance perspective.

Methods: We conducted a retrospective claims data analysis using the InGef Research Database (2013-2018). Cervical conizations in 18-45-year-old women were identified by OPS codes (5-671.0*/5-671.1*). For a subpopulation, subsequent conizations after a 90-day wash-out period and healthcare costs during a 24-month follow-up period (starting with an index conization) were assessed. Costs were compared (1:1:1 matching) in women with CIN diagnosis (ICD-10-GM codes N87.0, N87.1, N87.2 and/or D06) who underwent conization (study cohort 1)and women with CIN who did not undergo conization (study cohort 2) versus women with neither CIN nor conization (control group) as all-cause costs for outpatient care, inpatient care, outpatient pharmaceuticals, aids and remedies, and sick leave costs. Mean imputation was applied for missing aids and remedies (~20%) and sick leave data (~5-23%).

Results: Between 2013-2018, the annual number of 18-45 year old women who underwent conization ranged from 611,380 to 630,284, giving an annual conization rate of 2.4/1,000 in 2013 and 2.1/1,000 in 2018, with over 60% of the observed women with conizations between 31-45 years old. The subpopulation used for the analysis of subsequent conizations and healthcare costs included N=2,749 women. Of these, 2.91% underwent a subsequent conization three months or later (up to 24 months) after the initial conization. Mean total healthcare costs during the 24-months follow-up period were higher in both study cohorts (study cohort 1: €4,446, p<0.01; study cohort 2: €3,754, p=0.09) compared to the control group (€3,426) and were mainly driven by inpatient care (study cohort 1: €1,849, p<0.01; study cohort 2: €1,348, controls: €1,169, p=0.07) followed by outpatient care (study cohort 1: €1,418, p<0.01; study cohort 2: €1,339, p<0.01; controls: €1,170). The highest mean total cost difference was found in women between 36-45 years.

Conclusions: Our results highlight a substantial burden of cervical conizations, especially in women aged 30 and older. This burden leads to €1,020 and €328 higher healthcare costs in women with a CIN diagnosis with and without conization, respectively, compared to women without CIN in a two-year follow-up period.

Leite Sara
Portugal

Dias Leite Sara
Portugal

#3763

THE WERTHEIM-MEIGS HYSTERECTOMY IN SURGICAL TREATMENT OF CERVICAL CANCER: SIX YEARS' EXPERIENCE

35 - Conventional therapies

Dias Leite S[1], Veiga Guimaraes M[1], Vide M[1], Petiz A[1]

[1]IPO-Porto, Porto, Portugal

Background/Objectives: Cervical cancer is the third most common cancer among women. Surgical management is the primary therapy for most patients with early-stage cervical cancer. The Wertheim- Meigs surgery is an effective treatment for low risk patients with stage IA2, IB1, IB2 and IIA cervical cancer. Assess the treatment and follow-up of the patients when Wertheim-Meigs surgery has been performed for cervical cancer.

Methods: Retrospective observational study with descriptive data analysis of the patients who underwent Wertheim-Meigs surgery due to cervical cancer at the Portuguese Institute of Oncology - Oporto (IPO-Porto) between 2013 and 2018.

Results: During a six year period between 2013 and 2018, 70 patients underwent the Wertheim-Meigs surgery due to cervical cancer, with a median age of 49 years. The clinical FIGO stage was IA2 in 11%, IB1 in 83%, IB2 in 1.6% and IIA1 in 4.7% of the patients. A laparotomy surgery was performed in 89% of the cases. The vast majority of the patients did not present linfovascular invasion (73%) nor parametrial (90%). Six women (8,7%) had lymph node invasion, five with only one positive node and one patient with two. The majority did not have indication for adjuvant treatment, 29% underwent brachytherapy, 26% external radiotherapy and 1.4% chemotherapy. Squamous cell carcinoma was identified in 38 patients (54%), adenocarcinoma in 28 (40%), adenoid cystic carcinoma in 3 (4%) and adenosquamous carcinoma in 1 (1%). Two patients had disease recurrence (2,9%), one with adenoid cystic carcinoma and the other with adenocarcinoma. The minimum follow-up time in IPO-Porto was 5 years in the majority of the cases. Four deaths were reported (5,7%), with only one directly related to cervical cancer. This was a patient with adenoid cystic carcinoma with local recurrence and distant metastases identified 8 months post surgery, dying after a period of 37 months of follow-up.

Conclusions: The Wertheim Meigs surgery seems to be an effective treatment in the early stages of cervical cancer, with a low recurrence and mortality rate in the studied population.

Dostalek Lukas
Czech Republic

Dostalek Lukas
Czech Republic

#3631

The impact of lymph node micrometastases on disease free survival in cervical cancer patients - a retrospective subgroup study of the SCCAN (Surveillance in Cervical CANcer) project

26 - Cervical neoplasia

Cibula D[1], Borcinova M[1], Benesova K[2], Klat J[3], Falconer H[4], Kim S[5], Van Lonkhuijzen L[6], Lopez A[7], Isla Ortiz D[8], Landoni F[9], Kostun J[10], Ricardo D[11], Odetto D[12], Zapardiel I[13], Jarkovsky J[2], Javurkova V[3], Salehi S[4], Abu-rustum N[5]

[1]Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital, Central and Eastern European Gynecologic Oncology Group, (CEEGOG), Prague, Czech Republic, Prague, Czech republic

[2]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic, Brno, Czech republic

[3]Department of Obstetrics and Gynecology, Faculty of Medicine, University Hospital and University of Ostrava, Ostrava , Czech Republic, Ostrava, Czech republic

[4]Department of Pelvic Cancer, Karolinska University Hospital and Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden

[5]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA, New york, United states

[6]Department of Gynecological Oncology, Amsterdam University Medical Center—Center for Gynecological Oncology Amsterdam, Amsterdam, the Netherlands, Amsterdam, Netherlands

[7]Department of Gynecological Surgery, National Institute of Neoplastic Diseases, Lima, Peru, Lima, Peru

[8]Gynecology Oncology Center, National Institute of Cancerology Mexico, Mexico, Mexico, Mexico

[9]University of Milano-Bicocca,Department of Obstetrics and Gynecology, Gynaecologic Oncology Surgical Unit, ASST-Monza, San Gerardo Hospital, Monza, Italy, Monza, Italy

[10]Department of Gynaecology and Obstetrics, University Hospital Pilsen, Charles University, Prague, Czech Republic, Plzen, Czech republic

[11]Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States, Huston, United states

[12]Department of Gynecologic Oncology , Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano , Buenos Aires , Argentina, Buenos aires, Argentina

[13]Gynecologic Oncology Unit, La Paz University Hospital - IdiPAZ, Madrid, Spain, Madrid, Spain

Background/Objectives: The impact of lymph node (LN) micrometastases (MIC) in cervical cancer patients remains a controversial topic given their low incidence and good prognosis of patients managed by primary surgery. We aim to evaluate the prognostic significance of MIC and isolated tumour cells (ITC) in a large cohort of patients from the SCCAN retrospetive study (Surveillance in Cervical CANcer). SCCAN study analysed data from more than 4300 patients with early stage cervical cancer treated by primary surgery at 20 large tertiary institutions from Europe, North America, South America and Australia.

Methods: In this SCCAN sub-study, we included patients with early stage cervical cancer (T1a1 LVSI+ - T2b) treated between 2007 and 2016 with at least 1-year follow-up data availability, who were treated by primary surgery including sentinel lymph node (SLN) biopsy and in whom SLNs were processed by pathological ultrastaging protocol.

Results: Out of 969 included patients with at least 1 SLN detected, 174 (18%) had positive LN (Table 1). Maximal tumour diameter >2cm, positive LVSI, grade ≥ 2, uncommon histological type (neuroendocrine, sarcoma, etc.) and macrometstasis (MAC) or MIC in LN were factors associated with significantly decreased five-years disease free survival (DFS) (Table 2). MAC, MIC or ITC was the largest LN metastasis in 84 (9%), 59 (6%) and 31 (3%) cases respectively. Adjuvant (chemo)radiation was administred in 89%, 85% and 58% of patients with MAC, MIC and ITC. DFS reached 75%, 73% and 83% in patients with MAC, MIC and ITC compared with 90% in the N0 patients. Patients with MAC and MIC had significantly decreased DFS than those with N0 disease (HR=2.36 and 2.55).

Conclusions: Early-stage cervical cancer patients with MIC in pelvic LN have significantly decreased DFS. Their management should follow the same principles as in patients with MAC.

Lukas Dostalek

López Zarco Guillermo
Spain

Pingarrón Carmen
Spain

#3958

INMUNOMODULATION IN VIRAL PROCESSES OF THE CERVIX

05 - Immunology

Background/Objectives: The evolution of a viral process generally depends on the viral load and the response of the immune system. The immune response is a critical factor for eliminating the human papillomavirus (HPV) infection. As demonstrated in numerous studies, the progression of HPV infection and lesions is more frequent in women with a defect in the immune system response, and in those who are immunosuppressed especially by HIV or other immunodeficiencies. HPV infection trigger first the local activation of the innate immune response that would results in the activation of the adaptive immunity. However, we also know that HPV proteins E6 and E7 induce the transcription of immunosuppressive cytokines as a means of evading HPV the host immune system, that compromise and/or delay the induction of an adaptive immune response. Nowadays, prophylactic preventive vaccines are available and therapeutic one's are under development. However, modulation of the immune system is also a key complementary strategy against HPV. The present study has evaluated the benefits of nutritional supplementation with a casein hydrolysate-based formula, an important source of bioactive peptides that ensure a rapid assimilation of essential amino acid, in patients with high-risk (HR)-HPV infection.

Methods: An observational, prospective, multicentre, and controlled study have been carried out in Spain. A total of 118 patients have completed the study. Women from 20 to 65 years old with positive DNA test for at least one HR-HPV with normal, ASCUS or LSIL cytology were included. The diagnostic procedure was performed by liquid cytology and DNA extraction by multiplex PCR at 0 and 6 months. The supplemented patients' groups underwent blood tests to determine different immune parameters. Patients with casein hydrolysate-based formula supplementation received 1 dose of the formula every day for 6 months from the start of the study.

Results: Nutritional supplementation with the casein hydrolysate-based formula (Ditriamino®) in patients with HR-HPV,correlates with an immunomodulatory effect on both arms of the immune response: innate and adaptive.Our findings show that supplementation stimulates the systemic immune response by increasing the systemic levels of members of innate immunity, natural killer (NK) cells and adaptive immunity such as TCD8+, TCD4+ lymphocytes at 6 month. In parallel, we have also observed a significant shorter time to HPV clearance and significant efficacy in normalizing cervical cytology in the supplemented patients than in control at 6 months (74,6% vs. 35,6%, $p < 0.05$ and 67,4% vs. 41,9%, $p < 0.05$ respectively). Additionally, the nutritional supplementation in combination treatment with a topical immune response modifier (Imiquimod 5% cream) have shown a significant shorter resolution time of condylomas after 12 weeks and low recurrence rate after 6 months than in control patients under Imiquimod monotherapy.

Conclusions: The results of this study confirm that nutritional supplementation with casein hydrolysate-based formula (Ditriamino®) represents a well-tolerated and easily administered oral support that could help the own immune system of the patient to fight against HPV infection. It boosts the innate immune response as first line of defence and the cellular immune effectors of the adaptive immunity, accelerating the clearance of the virus, favoring the remission of lesions derived from HPV infection and preventing their progression.

FC08 - Vaccines 2

Senese Francesca
Italy

Senese Francesca
Italy

#3684

Eliminating cervical cancer in Italy: results from mathematical modeling of HPV vaccination impact and DNA screening

36 - Economics and modelling

[1]Msd Italy, Rome, Italy
[2]Merck , Kenilworth, nj, United states
[3]Department of Economics and Finance - University of Tor Vergata, Rome, Italy

Background/Objectives: Since the late 1990's, when it expanded organized cervical screening programs (OCSPs), Italy has been working on the reduction of cervical cancer (CC) incidence. In 2007, Italy was one of the first EU countries to introduce a national human papillomavirus (HPV) vaccination program with gender neutral offered since 2017. Several regions also have multicohort approach including 25 y.o.a. ladies catch-up and immunization offered to women treated for HPV lesions. For CC screening, HPV DNA screening (introduced in 2014) has become an increasingly important component of the national screening program becoming the standard from the age of 30. However, uptake and coverage of both interventions are heterogeneous across Italian regions. The WHO has defined three targets that are key for the elimination of CC as a public health problem (incidence below 4 per 100,000 women): 90% vaccination coverage, 70% coverage of screening, and 90% of women with cervical disease being treated. The aim of this study is to understand how these efforts are contributing to the elimination of CC in Italy on a national and subnational level, and to forecast what year elimination will be met.

Methods: A mathematical model of cervical HPV infection and disease was adapted to Italy on a national and sub-national level. The model accounts for historical changes in screening programs and HPV vaccination (including the transition to gender neutral vaccination, and a nonavalent vaccine) throughout Italy and was validated against documented drops in CC incidence following increasing coverage of OPSCs among target populations. At national and subnational levels, CC incidence was projected forward from 2021 and the year at which incidence reaches various thresholds of interest. Counterfactual scenarios were also run to ascertain the contribution of each intervention (HPV DNA screening and HPV vaccination) in achieving these thresholds.

Results: At the national level, screening alone, while responsible for significant near-term declines, is unlikely to lower CC incidence below 4 per 100,000 women. But when combined with HPV vaccination, this threshold is expected to be reached by approximately 2048. These results can vary among subnational regions.

Conclusions: Italy's efforts in CC screening and HPV vaccination have yielded significant benefits and will continue to drive CC incidence down over the next decades. Nevertheless, HPV immunization as a means of primary prevention is the key component of the strategy that will make the difference in whether elimination is reached, and higher vaccination coverage rates will contribute to an earlier year of elimination.

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Dolk Christiaan
Netherlands

Dolk Christiaan
Netherlands

#3493

THE PUBLIC HEALTH IMPACT AND COST EFFECTIVENESS OF GENDER NEUTRAL 9VHPV VACCINATION IN THE NETHERLANDS

36 - Economics and modelling

Dolk C[1], Sabale U[2], Palmer C[3]

[1]MSD, Haarlem, Netherlands

[2]Center for Observational and Real-World Evidence (CORE), MSD, Stockholm, Sweden

[3]Merck , Kenilworth, nj, United states

Background/Objectives: HPV vaccination targeting 12-year-old-girls is included in the National immunization program (NIP) since 2010, and uptake currently plateaus at approximately 60%. Since introduction, a bivalent human papillomavirus (2vHPV) vaccine against two HPV types 16/18 responsible for 70% of cervical cancer was used. In 2019, the Dutch Health Council recommended lowering the age of the primary vaccination cohort and the inclusion of boys in the NIP. Following this recommendation, starting in 2022, both 9-year-old boys and girls will be eligible for HPV vaccination.1 This study assesses whether a gender-neutral vaccination with a nonavalent HPV vaccine (9vHPV) against HPV types 6/11/16/18/31/33/45/52/58 is a cost-effective strategy in the Netherlands.

Methods: Using a previously published dynamic transmission model for HPV infections that has been adapted to the Netherlands, we performed a base line analysis assuming the program continues the current strategy of gender-neutral 2vHPV vaccination (with a switch to the 9-year-olds and compared the outcomes with those resulting from a strategy with 9vHPV vaccination in the same cohort.2,3 Various sensitivity analyses were performed, including assumptions of vaccination coverage rates (VCRs) and the degree of cross-protection. The analysis is performed from a healthcare perspective over a 100-year time horizon.

Results: Compared to 2vHPV vaccination, vaccination with a 9vHPV vaccine was estimated to significantly decrease the cumulative incidence of HPV 6/11/16/18/31/33/45/52/58-related diseases, averting over 3000 additional HPV related cancer cases, approximately two-thirds of which are averted cervical cancer cases, over the studied horizon,withover 1000 additional lives saved. Additionally, 9vHPV vaccination was estimated to avert over 1 million cases of genital warts and decrease the incidence of genital warts by over 80%. Incidence of both adult- and juvenile-onset of recurrent respiratory papillomatosis were reduced by approximately 95%, with a total of over 4000 averted cases. Compared to a 2vHPV vaccination strategy, 9vHPV vaccination was demonstrated highly cost-effective (ICER under €8000 per quality-adjusted life-years), which is robust according to sensivity analysisis results around VCRs.

Conclusions: 9vHPV vaccination can considerably decrease more HPV-related cancers and genital warts than the current 2vHPV vaccination program and is a highly cost-effective strategy.

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Munk Christian
Denmark

Munk Christian
Denmark

#3601

GIRLS-ONLY HPV VACCINATION - IMPACT ON THE HPV TYPE DISTRIBUTION IN YOUNG MEN

40 - Public health

Munk C[1], Reinholdt K[1], Kjaer A[1], Hemmingsen C[1], Oernskov D[2], Waldstroem M[2,3], Kjaer S[1,4]

[1]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen o, Denmark

[2]Department of Pathology, Vejle Hospital, Lillebaelt Hospital, Vejle, Denmark

[3]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

[4]Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background/Objectives: In Denmark, a girls-only HPV vaccination program has been in place since 2008-9. Subsequent catch-up programs for older girls/women mean that the HPV vaccination coverage in women born from 1985 until 2008 is around 70% across all birth cohorts. Since July 2019, HPV vaccination has been offered to boys aged 12 years. In Denmark, HPV vaccination is offered free-of-charge and in a call-recall system (invitation and reminder to those not responding). The objective of this study was to assess the overall HPV prevalence and the type distribution in younger men before the direct effect of HPV vaccination of younger boys becomes apparent.

Methods: We invited men who attended information days regarding military service at two barracks. In Denmark, all men are obliged by law to attend this information shortly after they turn 18 years. At random days from December 2019 to December 2020, 280 men were included in the study. They answered a shorter questionnaire with questions related to risk factors for HPV infection and a penile swap for subsequent HPV testing was collected. In conjunction with the penile swab, a physician assessed circumcision status and presence of genital warts. The penile swabs were stored at -80 degrees C. HPV testing was done with the Inno-Lipa Extra II (Fujirebio) which can detect 32 HPV types.

Results: The median age was 18 years with 94% being 18 to 20 years old. In all, 21 (7.5%) were circumcised and no one presented with genital warts. Forty men (14.3%) had not had their first sexual intercourse. The median number of sexual partners in the last 6 months was one partner with 76 (27.1%) having had two or more. Finally, 32 men (11.4%) reported to have been HPV vaccinated outside the program at their own expense. Altogether 129 men (46.3%) were HPV positive. Overall, 24.3% of the men had a high-risk HPV type, 23.9% had a low-risk type and 7.1% had an unidentifiable HPV type (HPV X). No infections with HPV types 6, 11, 16, 18, 31, and 45 were detected. The most frequent type was HPV 51 which was detected in 31 men (11.1%) followed by type 59 (8.2%) and type 66 (6.8%). Analyses related to e.g. vaccination status and sexual variables will be presented at the EUROGIN meeting.

Conclusions: The girls-only vaccination program in Denmark seems to a large degree having protected young men against the HPV types included in the licensed vaccines. The overall HPV prevalence is still high but consists largely of less carcinogenic HPV types.

De Bondt Daniël
Netherlands

De Bondt Daniël
Netherlands

#3766

THE IMPACT OF HPV VACCINATION ON HPV PREVALENCE, PRE-CANCERS, CANCERS: A SYSTEMATIC REVIEW ON OBSERVATIONAL AND MODEL OUTCOMES.

40 - Public health

Naslazi E[1], De Bondt D[1], De Kok I[1], Jansen E[1], Hontelez J[1]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands

Background/Objectives: HPV vaccination has been implemented in most high-income countries. With the new (partly) vaccinated cohorts approaching screening ages, policymakers need to re-evaluate how to shape screening for these cohorts. It will be vital to understand the impact of vaccination on the prevalence of high-risk HPV, pre-cancerous lesions, and/or cancers in vaccinated and unvaccinated women. Comparing observations to model predictions can give important insights into the validity of models and their predictions, and can help set benchmarks for improvement of modelling precision in the future.

Methods: We searched Cochrane Library, EMBASE, MEDLINE, Web of Science for studies published between 2005 to present. We performed three independent literature searches for studies that reported on effects of HPV vaccination in a high-income country: 1) Systematic reviews, 2) Observational studies performed after the last systematic review was published, and 3) Studies that used HPV transmission models. Studies were eligible if they reported both pre- and post-vaccination outcome figures on a population level, included vaccination coverage, and if they examined equal population characteristics before and after vaccination. Relative risk (RR) for HPV-related health outcomes was calculated comparing the pre-vaccination and post-vaccination periods. These risks were then compared to prevalence reductions found in the modelling studies.

Results: We identified a total of 7963 potential articles, and included five systematic reviews, 11 observational studies and 20 modelling studies in 18 different high-income countries. HPV prevalence, CIN and cervical cancer reduction were used as an outcome in different studies. All studies reported significant vaccination effectiveness in all three outcomes (mean RR: 0.30 for HPV, 0.51 for pre-cancers and 0.71 for cervical cancers). The effect was more heterogeneous for later disease outcomes. Most studies showed a relationship between vaccination coverage and effectiveness, with greater decreases in HPV-related outcomes with higher coverage. This relationship was also found among the modelling studies.

Conclusions: A combined assessment of both observed evidence and modelling predictions allows to more confidently evaluate the effects of HPV vaccination in high-income countries. This will assist policymakers in reshaping their screening programs.

Middeldorp Marit
Netherlands

Middeldorp Marit
Netherlands

#3708

Vaccine effectiveness against persistent genital HPV infections up to ten years after three doses of the bivalent HPV vaccine

40 - Public health

Joske H[1], Middeldorp M[1], Audrey J K[1], Prof Johannes B[2], Hester E D[1]

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands

[2]Department of Epidemiology , Amsterdam, Netherlands

Background/Objectives: In the Netherlands, the bivalent HPV vaccine (2vHPV) has been offered to preadolescent girls via the National Immunization Program in a three-dose (3D) schedule between 2010 and 2014, and was replaced by a two-dose schedule from 2014 onwards. We aimed to estimate vaccine effectiveness (VE) against HPV persistent infections among girls eligible for a catch-up campaign 3D immunization up to ten years post-vaccination.

Methods: Data were used from a longitudinal cohort study (HAVANA) in which participants were annually asked to fill out a questionnaire and provide a vaginal self-swab for HPV determination using the SPF10-LiPA25 assay. Vaccination status of participants was acquired through the national vaccination registration system. Adjusted VEs against persistent HPV16/18 and cross-protective type (HPV31/33/45) infections following 3D immunization were estimated using the Prentice Williams-Peterson total-time approach. Persistent infections were defined as two HPV positive samples for the same HPV type in two consecutive years, preceded by a negative sample. Additionally, adjusted VE estimates up to 5 years post-vaccination and 5-10 years post-vaccination were estimated for HPV16/18 and HPV31/33/45. VEs were adjusted for age, urbanization degree, contraceptive use and sexual activity.

Results: A total of 1635 girls were included in the VE analyses, of whom 875 (53.5%) were vaccinated according to a 3D schedule. Preliminary data showed an adjusted pooled VE against persistent HPV16/18 infections of 95.8% (95% CI, 86.6-98.7%), and 64.6% (95% CI, 37.6-79.9%) against HPV31/33/45. Moreover, VE against persistent HPV16/18 infections amounted to 100% (95% CI could not be estimated) and 93.2% (95% CI, 78.1-97.9%), respectively for less than 5 years and 5-10 years post-vaccination. These estimates amounted to 43.4% (95% CI, -48.3-78.4%) and 71.9% (95% CI, 42.6-86.2%) for HPV31/33/45.

Conclusions: We found high VE estimates following 3D immunization against persistent genital infections in women in a population-based observational study after a 10-year follow-up. Furthermore, we did not find any indication of waning against persistent HPV16/18 and HPV31/33/45 infections over time. Continued surveillance of the HPV vaccination program is important to monitor future changes in protection or shifts in HPV trends over time.

Man Irene
France

Man Irene
France

#3623

Evidence-based impact projections of single-dose human papillomavirus (HPV) vaccination in India

40 - Public health

Man I[1], Georges D[1], De Carvalho T[2], Saraswativ L[3], Bhandari P[3], Kataria I[3], Siddiqui M[3], Muwonge R[1], Berkhof J[2], Sankaranarayanan R[3], Bogaards J[2], Basu P[1], Baussano I[1]

[1]Early Detection, Prevention and Infections Branch, International Agency for Research on Cancer, Lyon, France

[2]Department of Epidemiology and Data Science, Amsterdam University Medical Center, location VUmc, Amsterdam, Netherlands

[3]RTI International, New delhi, India

Background/Objectives: Despite having the highest expected burden of cervical cancer worldwide, India still has limited access to HPV vaccination and cervical screening. Immunization by single-dose schedule could facilitate the scale-up of HPV vaccination in India and other low- and middle-income countries. Currently, evidence on the effectiveness of the single-dose schedule is expanding. In this work, we explore the impact of single-dose HPV vaccination in India and compare it to the impact of two-dose vaccination.

Methods: Based on Indian demographic and epidemiological data, and on data from the IARC India vaccine trial with 10-years follow-up, we constructed an HPV transmission model (EpiMetHeos) and adapted it to Indian states. Using the model, we projected the impact of HPV vaccination on the occurrence of HPV infection and cervical cancer incidence. Projections were obtained under different vaccination coverages, catch-up age ranges, as well as different scenarios of waning vaccine protection by single-dose vaccination.

Results: Under the base-case scenario, i.e., equal life-long vaccine protection by single-dose as compared to two-dose vaccination and 90% coverage, both single- and two-dose vaccination were projected to eliminate HPV 16 and 18 in the long-term and to provide some cross-protection to HPV 31, 33 and 45. Life-time risk (LTR) of cervical cancer was reduced by 70% in the first 5 routinely vaccinated cohorts and by 79% in the long term. The elimination threshold for age-standardized cervical cancer incidence rate (of 4 cases per 100,000 women) was reached throughout India, while an alternative threshold by standardized LTR (of 250 cases per 100,000 women born) was reached only in some Indian states with relatively low pre-vaccination LTR. Under scenarios with waning single-dose protection, vaccination could still reduce the LTR of cervical cancer by at least 50% if efficacy sustained above 75% for at least 20 years and vaccination coverage remained above 60%. Finally, under all considered scenarios with waning single-dose protection, vaccinating 10 routine and 10 catch-up cohorts with single-dose schedule had a higher impact on cancer cases than using the same number of doses to vaccinate only 10 routine cohorts with two doses.

Conclusions: Capitalizing on data on Indian cervical cancer epidemiology and from the IARC India vaccine trial, we demonstrated the potential of single-dose HPV vaccination and its comparative advantage to two-dose vaccination in India. Our context-specific projections could provide guidance to policymakers in deciding whether and how to implement cervical cancer preventive measures.

Daniels Vincent
United States

Vincent Daniels
United States

#3998

ESTIMATION OF HPV VACCINE MODEL PARAMETERS AND UNCERTAINTY FROM INTERIM ANALYSIS OF KEN-SHE TRIAL

36 - Economics and modelling

Vincent D[1], Kunal S[1], Cody P[1], Ya-ting C[1]

[1]Merck , Kenilworth, nj, United states

Background/Objectives: Modeling the impact of off-label single dose (OLSD) vaccination programs requires parameters characterizing the effect of the vaccine on the target population. These parameters and their associated uncertainty are ideally derived from vaccine randomized controlled clinical trial (RCT) data analyzed in the context of a specific vaccination model. The KEN-SHE trial1 in Kenya is one of the first RCTs specifically designed to study the efficacy of OLSD on prevention of HPV infections among adolescents and young women.

Methods: We employed a Markov chain Monte Carlo (MCMC) method to generate a probability distribution of model parameter values using the pooled HPV 16/18/31/33/45/52/58 KEN-SHE and control arm interim analysis of 18-month data2. The resulting parameter values can be used to characterize effectiveness in models and provide an uncertainty distribution for probabilistic sensitivity analyses (PSA) of vaccine model outcomes. We first fit a 2-parameter, constant rate compartmental model with vaccinated-partially protected, vaccinated susceptible, and infected compartments. We estimate a joint distribution of the model's constant rates: "degree of protection", ψ, defined as the fraction of exposed vaccinated people that become infected (breakthrough infection); and "duration of protection", $\tau 1/2$, which is inversely proportional to the rate at which vaccinated people become completely susceptible - specifically, the time it would take for ½ the vaccinated population to lose protection. We also explore sensitivity to the vaccine model structure assumptions.

Results: For the simple 2-parameter vaccine model the "most probable" parameter pair is (ψ, $\tau 1/2$) = (93.0%, 8.7 years) with 95% CI for ψ and $\tau 1/2$ of 74.2% to 99.3% and 1.5 years to 68 years, respectively. The parameters are correlated such that lower degree of protection is more likely associated with longer duration and vice versa. Similar results are obtained for other vaccines models.

Conclusions: Our results show that while the KEN-SHE provides evidence of high OLSD efficacy at 18 months, there is substantial uncertainty in the long-term effectiveness. In addition, the trial data provides a scientifically rigorous foundation for estimating model parameter values and uncertainty distributions that are critical inputs for health and economic models used to inform vaccination policy decisions. As more efficacy data on OLSD from RCTs become available in the coming years improved estimates (and more certainty) of these important model parameter inputs will be possible.

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FC11 - HPV testing

Marini Bruna
Italy

Marini Bruna
Italy

#3769

A new PCR-based detection methodology for Human Papillomavirus genotyping on cervical brushes and self-collected vaginal samples

14 - Genotyping

Avian A[1,2], Clemente N[3], Mauro E[1], Isidoro E[4], Di Napoli M[4], Dudine S[4], Del Fabro A[3], Morini S[3], Perin T[3], Giudici F[5], Cammisuli T[6], Foschi N[1], Mocenigo M[1], Montrone M[1], Modena C[1], Polenghi M[1], Puzzi L[1], Riva E[8], Angeletti S[8], Ciccozzi M[8], Castriciano S[9], Pachetti M[10], Zella D[11,12], Centonze S[13], Gerin D[14], Banks L[15], Marini B[1], Canzonieri V[5,6], Sopracordevole F[3], Zanconati F[4,5], Ippodrino R[1]

[1]Ulisse BioMed, Trieste, Italy

[2]University of Nova Gorica, Molecular Genetics and Biotechnology PhD study programme, Nova gorica, Slovenia

[3]Ginecologia Oncologica, IRCCS - Centro di Riferimento Oncologico (CRO) (Istituto Nazionale Tumori – National Cancer Institute), Aviano, Italy

[4]Azienda Sanitaria Universitaria Giuliano Isontina UCO/SC Anatomia e Istologia Patologica, Cattinara Hospital, Trieste, Italy

[5]University of Trieste, Department of Medicine, Surgery and Health Sciences, Trieste, Italy

[6]Anatomia Patologica, IRCCS – CRO (Istituto Nazionale Tumori - National Cancer Institute), Aviano, Italy

[7]Institut Ruđer Bošković, Zagreb, Croatia

[8]Policlinico Universitario Campus Biomedico, Rome, Italy

[9]Copan Italia Spa, Brescia, Italy

[10]Burlo Garofalo, Trieste, Italy

[11]Institute of Human Virology, Department of Biochemistry and Molecular Biology, School of Medicine, University of Maryland, Baltimore, United states

[12]Member of the Global Virus Network, Baltimore, United states

[13]Azienda Sanitaria Universitaria Giuliano Isontina , Clinical research Unit, Trieste, Italy

[14]Azienda Sanitaria Universitaria Giuliano Isontina , Cervical Cancer Screening Coordination Unit, Trieste, Italy

[15]International Centre for Genetic Engineering and Biotechnology, Trieste, Italy

Background/Objectives: The study aims at evaluating the diagnostic performance of HPV Selfy, a new PCR-based detection and genotyping methodology for high risk Human Papillomavirus (HPV) on clinician-collected cervical brushes and self-collected vaginal samples in a screening population. HPV Selfy is able to perform full high risk HPV genotyping in the same PCR reaction.

Methods: From September 2018 to February 2019 all the women consecutively referring to Azienda Sanitaria Integrata Giuliano Isontina (ASUGI - Trieste, Italy) and to CRO - National Cancer Institute (Aviano, Italy) for the Italian cervical cancer screening programme were invited to participate in the study (n=1143). Eligible women were asked to perform both a vaginal self-sampling analyzed with our new PCR-based detection methodology for HPV and a clinician-collected cervical brush for Pap smear, analysed with the Hybrid Capture® 2 DNA test analysis. All the women enrolled were asked to fill a proper questionnaire about self-sampling acceptability. Moreover, a second group of women (n=500), whose traditional screening test was delayed because of the COVID-19 pandemic, was enrolled in the period February 2021-April 2021. Women were mailed a kit at home for self-collection and returned the sample to the hospital for the analysis with the HPV Selfy test.

Results: HPV Selfy was clinically validated on cervical brushes and vaginal swabs, reaching non-inferior performance to the reference test.HPV Selfy shows high concordance between self-collected and expert-collected specimens for HPV detection. According to the questionnaire response, 98.4% of women agreed that self-sampling test format was easy and effective. Genotyping analysis showed that prevalence of oncogenic HPV types was 9%; the five most frequent high risk HPV types detected in the cytology-negative screening population were HPV16 and HPV31, followed by HPV39, HPV51 and HPV66. On the other hand, in the CIN2+ population, HPV16 was the predominant strain followed by HPV31 and HPV58. Through a second prototype assay, able to genotype also 10 low-risk and probably high risk HPVs, we found a low and probable high risk HPV prevalence of 10% in the screening population.

Conclusions: The study demonstrated that HPV Selfy is potentially suitable for primary screening purposes performed on clinician-collected samples, providing also full genotyping information in the same reaction. According to several studies, genotyping information will become valuable for future triage strategies development. Despite hrHPV genotyping has not achieved widespread acceptance among clinicians, significant differences have been observed in the oncogenicity of hrHPV genotypes. HPV Selfy can also be used in combination with self-sampling tools to rescue women difficult to reach with traditional screening methods. HPV self-sampling could be an attractive solution to increase women's participation, regardless of age, education level, and other possible social parameters. It has been also demonstrated that self-sampling will be particularly relevant nowadays, when COVID-19 pandemic deeply impacted the effectiveness of hospital-based organized screening programmes.

Muresu Narcisa
Italy

Sechi Illari
Italy

#3491

Comparison of traditional and rapid nucleic acid extraction using a non-alcohol-based medium for vaginal self-samples

09 - HPV testing

Sechi I[1], Del Rio A[1], Muresu N[1], Dettori A[1], Usai M[1], Cossu A[1], Cocuzza C[1], Muroni M[1], Castriciano S[3], Piana A[1]

[1]Department of Medical Surgery and Experimental Sciences, University of Sassari, Sassari, Italy

[2]Department of Medicine and Surgery, University of Milano-Bicocca,, Monza, Italy

[3]Copan Italia Spa, Brescia, Italy

Background/Objectives: Vaginal self-collected sample is a convenient and economical method, as well as a useful strategy to reach women who do not participate to cervical cancer screening. Although the higher sensitivity of the HPV-DNA testing, the accuracy of the test is related to the stability of the swabs during transport and to the elution medium, particularly for vaginal self-collection. Moreover, new approaches in HPV screening, as rapid thermal nucleic acids extraction (RTNAE), could be useful in reducing cost and time of analyses. MSwabTM is a non-alcohol-based medium for the collection, and storage of clinical specimens, suitable for traditional NA extraction or RTNAE. The aim of the present study was to evaluate the analytical performance of both traditional and RTNAE methods using dry self-collected FLOQSwabs® eluted in MSwabTM medium (COPAN Italia) for high-risk HPV detection.

Methods: A total of 194 women were enrolled, within regional LILT (Italian League against Tumor) project. Dry self-collected FLOQSwabs® samples, were suspended in 2 mL of MSwabTM and processed at the Molecular Epidemiological laboratories of University of Sassari (Sardinia, Italy). Traditional DNA extraction was carried out firstly by an automated system (Seegene AdvanSureTM E3) and analyzed by AnyplexTM II HPV HR (Seegene). All high-risk HPV-positive and some HPV-negative MSwab-samples, stored at room temperature and at -20°C, were processed with a RTNAE at 98°C/5mins and analyzed for high-risk HPV. Diagnostic agreement was assessed with the Cohen's K statistic.

Results: A total of 15.5% (30/194) of samples resulted positive after traditional extraction method. In the 30 HPV-positive and 10 HPV-negative, RTNAE tested after storage at RT (mean days of storage: 177) and storage at -20°C, all negative samples and 26/30 (86.7%) of HPV-positive were confirmed. Overall, an excellent agreement was detected among the two extraction methods and storage conditions: - After RT storage: 90% agreement (k=0.77, p<0.0001) between Traditional DNA extraction vs RTNAE methods. - After -20°C storage: 90% agreement (k=0.77, p<0.0001) between Traditional DNA extraction vs RTNAE methods. - RTNAE methods after RT vs -20 °C storage: 95% agreement (K= 0.89, p<0.0001).

Conclusions: The present study showed as MSwabTM medium was a reliable and stable medium for elution and storage of dry vaginal self-collected FLOQSwabs®. These preliminary results showed a comparable high diagnostic accuracy of HPV-DNA between automated and RTNA extraction. MSwabTM direct-rapid thermal extraction, improves results turnaround time and saves costly extraction reagents. A non-alcohol medium for rapid and traditional nucleic acids extraction for detection of HPV in vaginal self-collected samples.

Muresu Narcisa Narcisa Muresu
Italy

#3398

New tool in cervical carcinoma prevention: a non-alcohol based medium for the elution of dry self-collected vaginal samples

09 - HPV testing

[1]University of Sassari, Sassari, Italy
[2]University of Milano Bicocca, Milano, Italy
[3]COPAN ITALIA, Brescia, Italy

Background/Objectives: Vaginal self-sampling is a cost-effective way to increase participation in cervical cancer screening, being a reliable instrument for HPV detection. Different collection devices, in dry or wet storage conditions, and elution in ethanol- or molecular-based buffers have been employed for HPV test using vaginal self-samples. In order to assess the optimal storage and transport conditions, for vaginal self-sampling, we evaluated the stability of dry self-collected FLOQSwabs® specimens transported at ambient temperature, resuspended in eNAT® medium (Copan Italia) and analyzed for HPV-DNA genotyping.

Methods: Into the LILT (Italian League against Tumor) project, a total of 177 samples were self-collected and analyzed at the Molecular Epidemiological laboratories of University of Sassari (Italy). All self-collected FLOQSwabs® samples were suspended in 2 mL of eNAT®, a molecular medium that stabilizes nucleic acids, and inactivates infectivity. DNA extraction was performed by an automated system (Seegene AdvanSureTM E3 System) and the AnyplexTM II HPV HR (Seegene) assay was used for HPV testing. Time of dry storage and HPV-DNA results were collected in an electronic database

Results: 17% (30/177) of FLOQSwabs® self-samples, resuspended in eNat® medium, were positive for at least one genotype of HPV of those 19 (63.3%) showed multiple HPV genotypes. The most common genotypes detected were HPV-56, 31, 51, 18 and 52. No "invalid" results were detected. The mean number (±SD) of days between samples collection and resuspension in medium, was 18.2 (±10.5); 36 swabs were stored dry for < 7 days, 19 for < 2 weeks, 39 for < 3 weeks, and 83 for over 21 days (21-48 days). No significant differences in HPV positivity were observed in relation to storage days, with a percentage of detection in accordance with the HPV prevalence reported in previous studies.

Conclusions: Vaginal self-collection is regarded a practical alternative for HPV analyses in cervical cancer screening program. Moreover, our preliminary results showed a high reliability of dry FLOQSwabs®, after ~1 month, and a significant stability for swabs eluted in eNAT® medium, suggesting their potential application in prevention strategies.

Del Rio Arcadia
Italy

#3498

Vaginal self-sampling as a tool for the prevention of cervical cancer

11 - Screening for women difficult to reach

Dettori A[1], Sechi I[1], Muresu N[1], Usai M[1], Cossu A[1], Muroni M[1], Castriciano S[2], Cocuzza C[3], Piana A[1]

[1]Department of Medical Surgery and Experimental Sciences, University of Sassari, Sassari, Italy

[2]Copan Italia SpA, Brescia, Italy

[3]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Background/Objectives: Human papillomavirus (HPV) infection is the major cause of cervical cancer. An effective approach for cervical cancer screening is the use of vaginal self-sampling in HPV-DNA testing, based on its accuracy and sensitivity. Moreover, use of vaginal self-collection device could improve the participation to cervical screening programs. The present study, organized by LILT (Italian League Against Tumors) and University of Sassari (Sardinia, Italy), aimed to increase the adhesion of hard-to-reach women to screening program and identify the potential population target, examining demographic and clinical characteristics of participants.

Methods: From April to July 2021, the participants received a kit containing instruction for use, a vaginal self-sampling device (FLOQSwabs®, Copan Italia) and a questionary assessing the ease of use of the collection device and the acceptability of vaginal self-collection. Overall, 371 women returned the questionary and a FLOQSwabs®. All dry swabs were processed for DNA extraction and analysed by PCR, using AnyplexTM II HPV HR Detection Kit (Seegene) that detects 14 high-risk HPV genotypes, at the Molecular Epidemiology laboratory of University of Sassari (Sardinia, Italy).

Results: The participating women were 371 (mean age of 42.7 years; SD ±11.4); 16.1% (60/371) of samples were HPV positive and the most common genotypes were 56, 31, 18 and 51. No invalid results were detected. Co-infection was reported in 33.3% (20/60) of samples. Among the 60 HPV-positive women, 20% (12/60) declared they never received a Pap test. 30.7% and 7.3% of single and married women were HPV-positive, respectively. The highest HPV positivity (27%) was detected in women under 35 years. FLOQSwabs® was found easy to use, self-collection was preferred to clinician collection by ~58% of participants, with variations related to different geographical areas.

Conclusions: The present study confirmed that vaginal self-sampling represents a valuable and well-accepted method in cervical cancer screening. HPV positivity rate and genotypes detected confirmed data previously reported in our setting. The questionnaire highlighted the acceptability of vaginal self-sampling with FLOQSwabs®, and the differences recorded could be associated with the quality and closeness to screening centres in Sardinian region. Self-sampling may increase screening participation, particularly among "non-adherents" women, overcoming practical, economic, and cultural barriers.

Marini Bruna
Italy
Marini Bruna
Italy

#3942

Clinical validation of full genotyping HPV Selfy assay according to the international guidelines for HPV test requirements for cervical cancer screening on clinician collected and self-collected samples.

14 - Genotyping

Marini B[1], Avian A[1,2], Clemente N[3], Mauro E[1], Isidoro E[4], Di Napoli M[4], Dudine S[4], Del Fabro A[3], Morini S[3], Perin T[3], Giudici F[5], Cammisuli T[6], Foschi N[1], Mocenigo M[1], Montrone M[1], Modena C[1], Polenghi M[1], Puzzi L[1], Valenti G[1], Sola R[1], Zanolla S[1], Vogrig E[1], Riva E[8], Ciccozzi M[8], Angeletti S[8], Castriciano S[9], Pachetti M[1,10], Zella D[11,12], Petti M[1], Centonze S[13], Gerin D[14], Banks L[15], Canzonieri V[5,6], Sopracordevole F[3], Zanconati F[4,5], Ippodrino R[1]

[1]Ulisse BioMed, Trieste, Italy

[2]2University of Nova Gorica, Molecular Genetics and Biotechnology PhD study programme, Nova gorica, Slovenia

[3]Ginecologia Oncologica, IRCCS - Centro di Riferimento Oncologico (CRO) National Cancer Institute , Aviano, Italy

[4]Azienda Sanitaria Universitaria Giuliano Isontina UCO/SC Anatomia e Istologia Patologica, Cattinara Hospital, Trieste, Italy

[5]University of Trieste, Department of Medicine, Surgery and Health Sciences, , Trieste, Italy

[6]Anatomia Patologica, IRCCS – CRO (Istituto Nazionale Tumori - National Cancer Institute), Aviano, Italy

[7]Institut Ruđer Boškovic, Zagreb, Croatia

[8]University of Campus Biomedico, , Roma, Italy

[9]Copan Italia, Brescia, Italy

[10]Burlo Garofalo, Trieste, Italy

[11]Institute of Human Virology, Department of Biochemistry and Molecular Biology, School of Medicine, University of Maryland, Baltimore, United states

[12]Member of the Global Virus Network, Baltimore, United states

[13]Azienda Sanitaria Universitaria Giuliano Isontina , Clinical research Unit, Trieste, Italy

[14]Azienda Sanitaria Universitaria Giuliano Isontina , Cervical Cancer Screening Coordination Unit, Trieste, Italy

[15]International Centre for Genetic Engineering and Biotechnology, , Trieste, Italy

Background/Objectives: The study aims at evaluating the diagnostic performance of HPV Selfy, a PCR-based DNA test for the detection and full genotyping of 14 high-risk Human Papillomavirus, in a single reaction, on clinician-collected cervical specimen and self-collected vaginal samples in a primary cervical cancer screening population, according to international guidelines.

Methods: In 2018 and 2019 women consecutively referring to Azienda Sanitaria Integrata Giuliano Isontina (ASUGI - Trieste, Italy) and toCRO - National Cancer Institute (Aviano, Italy) for the Italian cervical cancer screen program were invited to participate to the study. Eligible women were asked to perform both a vaginal self-sampling analyzed with HPV Selfy (Ulisse BioMed) and a clinician-collected cervical brush for Pap smear, analyzed both with the Hybrid Capture® 2 DNA test (HC2) (Qiagen) and HPV Selfy. As required by guidelines, a non-inferiority test was conducted to compare the clinical performance of HPV Selfy with the reference test. Meijer's guidelines for validation of HPV test for primary cervical cancer screening, and VALHUDES protocol for validation of the assay on self-collected samples.

Results: The study demonstrates that HPV Selfy clinical sensitivity and specificity are non-inferior to those of HC2. In particular, by analysis of a total of 889 cervical liquid-based cytology specimens from a cervical cancer screening population, of which 98 were from women with histologically diagnosed high grade cervical lesion (CIN2+), HPV Selfy showed relative sensitivity and specificity for CIN2+ of 0.98 and 1.00 respectively (non-inferiority score test: P=0.01747 and P=0.00414, respectively). In addition, an adequate intra- and inter-laboratory reproducibility has been reached by the test.Moreover, we demonstrated that the performance of HPV Selfy on self-collected vaginal swabs was non-inferior to the performance obtained on clinician-collected cervical brushes (0.92 relative sensitivity and 0.97 relative specificity). Finally, exploiting the genotyping capability of HPV Selfy test, we described HPV types prevalence in the study population. The most frequent high-risk HPV types detected in the cytology-negative screening population were HPV31 and HPV58, followed by HPV59. On the other hand, in the CIN2+ population, HPV16 was the predominant strain followed by HPV31 and HPV58.

Conclusions: In conclusion, this study demonstrates that the full genotyping test HPV Selfy is clinically non-inferior to HC2. The clinical performance and reproducibility of the assay meet the international criteria for validation of a high-risk HPV DNA test for cervical cancer screening purposes according Meijers's guidelines. Moreover, we demonstrated that HPV Selfy is also validated on self-collected samples for primary screening purposes, satisfying the requirements indicated by VALHUDES protocol. The study confirmed that self-sampling could be an attractivesolution to increase women's participation to cervical cancer screening programs. Self-sampling could be particularly relevant nowadays, whenCOVID-19 pandemic deeply impacted the effectiveness of hospital-based organized screening programs. In addition, HPV Selfy provides also full genotyping information in the same PCR reaction, that can be valuable for future triage strategies development since significant differences have been observed in the oncogenicity among different high risk HPV genotypes.

Castriciano Santina
Canada

Santina Castriciano
Italy

#3544

VALIDATION OF MSWABTM MEDIUM FOR THE ELUTION OF FLOQSWABS® FOR HUMAN PAPILLOMAVIRUS (HPV) DETECTION ON SIX COMMERCIAL PCR-BASED HPV ASSAYS

09 - HPV testing

Santina C[1], Marco H[1], Ivy N[1], David H[1]

[1]COPAN Italia SpA, Brescia , Italy

Background/Objectives: Vaginal self-collection has been advocated to improve women's participation to Human Papillomavirus (HPV) based cervical cancer screening programs. Currently, self-collected swabs are eluted in alcohol-based media, which is flammable, toxic, and costly to transport, and the use of different elution volumes can result in sensitivity variability. A medium to elute self-collected swabs that support HPV stability at different temperatures and is compatible with clinically validated commercial PCR-based HPV assays is necessary. MSwabTM is a non-alcohol-based medium validated for viral nucleic acid amplification assays. Current evidence demonstrates that self-collected specimens are non-inferior to clinical collected specimens for the detection of HPV. The aim of this study was to evaluate the performance MSwabTM medium for the detection of HPV with six commercial clinical validated PCR-based HPV assays using the PROCEEDxTM FLOQ® Swab controls.

Methods: In this study PROCEEDxTM FLOQ® Swab controls (HPV16, HPV18, HPV45, and Negative), produced by MicroBix Biosystems (Mississauga, Ontario, Canada), were used to simulate the elution of self-collected FLOQSwabs® in MSwabTM Medium (COPAN Italia, Brescia, Italy). Five of each PROCEEDxTM FLOQ® Swab controls were eluted in 3 ml MSwabTM medium by swirling for 20 seconds before removing the swab. All samples were assessed for the presence of HPV genotypes using the Abbott Alinity m on the Alinity m, Abbott Realtime on the m2000, Qiagen NeuMoDx on the NeuMoDx 96, Roche cobas 4800 on the cobas 4800, Roche cobas on the cobas 6800, and Seegene HPV28 on the STARlet/CFX systems, assays that are clinically validated for HPV detection. Testing was undertaken at the VCS Pathology Molecular Microbiology Laboratory.

Results: HPV16, HPV18, HPV45, and Negative PROCEEDxTM FLOQ® Swab controls in MSwabTM medium obtained a 100% sensitivity, specificity, negative and positive predictive values on the Alinity m, Realtime, NeuMoDx, cobas 4800, cobas, and HPV28 assays.

Conclusions: Data obtained in this evaluation, using MicroBix HPV and Negative PROCEEDxTM FLOQ® Swab controls eluted in COPAN MSwabTM medium, demonstrated 100% concordant performance using the Abbott Alinity m, Abbott Realtime, Qiagen NeuMoDx, Roche cobas 4800, Roche cobas, and the Seegene HPV28 assays for HPV detection. These data support the use of FLOQSwabs® in MSwabTM medium for detection of HPV using commercial clinically validated PCR-based assays.

Dhillon Sharonjit Kaur
Belgium

Dhillon Sharonjit Kaur
Belgium

#3606

CLINICAL VALIDATION OF HPV OncoPredict® SCR AND QT ASSAYS USING THE VALGENT-2 FRAMEWORK

09 - HPV testing

Dhillon S[1], Giubbi C[2], Cuschieri K[3], Cocuzza C[2]

[1]Unit of Cancer Epidemiology/Belgian Cancer Centre, Brussels, Belgium

[2]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

[3]3Scottish HPV Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, United kingdom

Background/Objectives: Background: Assessment of emerging HPV assays for their use in cervical cancer screening is vital. HPV OncoPredict® SCR and QT (Hiantis Srl) are two independent multiplex real-time PCR assays targeting HR-HPV E6/E7 DNA comprising a "partial" genotyping screening assay (SCR) and a "full" genotyping, normalized viral load (QT) assay. OncoPredict® SCR identifies HPV16 and HPV18 separately and 11 other hrHPV types in aggregate while OncoPredict® QT detects 12 high risk (HR) HPV types independently. The assays can be used either alone or in combination, as a two-step reflex testing allowing HR-HPV genotype-specific viral load determination in screen-positive samples. Quality controls for sample adequacy, the efficiency of nucleic acid extraction and PCR inhibition are included in the testing. Objectives: To evaluate the clinical performance of the HPV OncoPredict® SCR and QT using the international validation of HPV Genotyping Tests (VALGENT-2) framework.

Methods: Methods: The VALGENT-2 panel consists of 1,300 cervical liquid-based cytology (LBC) samples from women aged 20-60 attending the Scottish cervical cancer screening programme (1000 consecutive samples from routine screening enriched with 300 cytological abnormal samples). Disease was defined as histologically confirmed CIN2+ (n= 95 [denominator for sensitivity]), whereas two consecutive negative cytology results were accepted as a proxy for non-disease (n=721 [denominator for specificity]). Performance relative to GP5+/6+- PCR-EIA (standard comparator test) was assessed by a non-inferiority test.

Results: Results: The relative sensitivity and specificity for CIN2+ of OncoPredict® SCR vs GP5+/6+-PCR-EIA were 1.01 (95% CI, 0.99-1.03) and 1.02 (95% CI, 1.00-1.04). The results for OncoPredict® QT vs GP5+/6+-PCR-EIA were similar with a relative sensitivity of 1.01 (95% CI, 0.99-1.03) and relative specificity of 1.03 (95% CI, 1.0-1.06). The p-value for all the tests of non-inferiority was pni ≤0.001. Both assays also showed non-inferior accuracy when restricted to women aged 30 years or older.

Conclusions: Conclusions: HPV OncoPredict® SCR and QT assays fulfil the clinical accuracy criteria for use in cervical cancer screening. Acknowledgements: HPV OncoPredict® assays were developed as part of a European Commission funded SME Instrument Phase 2 Project (Grant agreement ID: 806551).

Eklund Carina
Sweden

Eklund Carina
Sweden

#3704

INTERNATIONAL QUALITY ASSURANCE OF HPV DNA GENOTYPING SERVICES: THE 2021 GLOBAL HPV DNA PROFICIENCY STUDY

09 - HPV testing

Eklund C[1], Lagheden C[1], Dahlin Robertsson K[2], Forslund O[3], Arroyo Mühr L[1], Dillner J[1]

[1]Karolinska Institutet, Stockholm, Sweden

[2]EQUALIS, Uppsala, Sweden

[3]Skane University hospital, Lund, Sweden

Background/Objectives: Objective: The International Human Papillomavirus (HPV) Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping. This international HPV DNA genotyping study issued in 2021 assesses the proficiency of the different HPV typing assays used routinely in laboratories worldwide as well as the performance of the laboratory.

Methods: Method: Participating laboratories were asked to perform HPV typing using one or more of their usual assays on 41 coded samples composed of purified whole genomic plasmids of sixteen HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a and 68b) in a background of human cellular DNA. Proficient typing requires detection in both single and multiple infections of 50 International Units of HPV 16 and HPV 18 DNA/ 5ml and 500 genome equivalents in 5 ml for the other types, with no false positive results.

Results: Results: The 2021 proficiency study had a record high number of participants: 161 panels were distributed to 138 laboratories worldwide: Most participants are from laboratories in Asia and Europe. Participating laboratories were both public health laboratories, research laboratories and diagnostic test manufacturers.

Conclusions: Implications and Impact: A continuing and increasingly popular global proficiency program promotes comparability and reliability of HPV genotyping assay performance worldwide.

Brautigam Karen
Germany

Bräutigam Karen
Germany

#3318

FREQUENCY, DISTRIBUTION, AND CORRELATION OF HPV IN DIVERSE ANOGENITAL AND ORAL SAMPLES

09 - HPV testing

Bräutigam K[1], Meier S[1], Meneder S[1], Polack S[1], Köster F[1], Rody A[1], Baum S[2]

[1]Department of Gynecology and Obstetrics, Medical Center Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

[2]Gynecology of MVZ Westpfalz, Kaiserslautern, Kaiserslautern, Germany

Background/Objectives: Human papilloma virus (HPV)-associated cancers increased world-wide in the last years. In addition to cervical cancer (CC), where HPV infections are attributable in >90 % of all cases, also other anogenital and oropharyngeal cancers are related to HPV infection. Furthermore, a high association with HPV was reported for intraepithelial neoplasia (INs) of the different anogenital areas.

Methods: In this study cervical, vaginal, vulvar, anal, and oral samples were collected from 509 women visiting our dysplasia consultation. DNA was isolated and full HPV genotyping (18 high risk [HR] and 12 low risk [LR] HPV types) was performed using EUROArray HPV.

Results: HR HPV (+/- LR HPV) was detected in 61.6% of cervical, 62.5% of vaginal, 64.3% of vulvar, 60.4% of anal, and in 14.6% of oral samples. HPV 16 showed the highest prevalence in all areas (cervix 45.7%, vagina 50.0%, vulva 53.9%, anus 54% and oral 79.7%). Besides HPV 16, HPV 31 was found most frequently (17.3%) followed by HPV 52 (12.0%), HPV 53 (11.3%), and HPV 18 in 9,0% in cervical, HPV 31 (16.0%), HPV 53 (13.8%), HPV 52 (12.6%), and HPV 39 (9.4%) in vaginal, HPV 53 (17.7%), HPV 31 (15.8%), HPV 52 (10.8%), and HPV 51 (8.7%) in vulvar, HPV 53 (18.9%), HPV 31 (11.3%), HPV 73 (10.3%), and HPV 51 (9.6%) in anal as well as HPV 53 (14.9%), HPV 51 (9.5%), and HPV 31 and 73 (4.1% each) in oral samples. A substantial to almost perfect concordance for most of the HPV types was examined in the cervical, vaginal and vulvar samples, and moderate to substantial concordance between those and anal samples. A good correlation was shown for high percentage of HR HPV infection in CC and HSIL (high squamous intraepithelial lesion) (CIN2/3) compared to lower HR HPV infection in LSIL (low SIL) (CIN 1) and CIN 0/normal samples.

Conclusions: As anticipated, HPV 16 showed the highest prevalence in all investigated areas. In cervical and vaginal samples, HPV 31 is frequent, while HPV 18 was detected rarely in all areas. Interestingly, HPV 53 could often be detected in different areas. As expected, the prevalence of HPV and HR-HPV infections were higher in women with precancerous lesions (CIN/VaIN /VIN ≥ 2) and carcinoma compared to women with normal cytology.

Da Silva Isabel Cristina Bandeira
Brazil

Wendland Eliana
Brazil

#3706

The Quality of Anal Sampling for HPV Genotyping: Experience of an Epidemiological Study

14 - Genotyping

Bandeira I[1], Kops N[1], Comerlato J[1], Bessel M[1], Moreno Alves De Souza F[2], Mendes Pereira G[2], Wendland E[1,3]

[1]Hospital Moinhos de Vento, Porto alegre, Brazil

[2]Ministry of Health, Department of STIs, AIDS and Viral Hepatitis , Brasília, Brazil

[3]Federal University of Health Science of Porto Alegre, Porto alegre, Brazil

Background/Objectives: High-risk HPV anal infection is associated with anal cancer. Screening for anal HPV among men who have sex with men (MSM) are crucial due to the increased incidence of anal cancer in this population. Therefore, we aimed to evaluate the quality of the anal self-sampling and associated factors in an epidemiological study.

Methods: We analyzed data from a cross-sectional, multicentric study about the prevalence of HPV among MSM in Brazil (SMESH study). Participants were instructed to self-collect HPV samples with a single Dacron swab soaked with saline solution. They swab must be introduced around 3 cm into the anal canal and rotate it 360 degrees at least twice. Sample collection was done under health professionals' supervision. The samples were submitted to DNA extraction (MagNA Pure LC 2.0 System, Roche) and subsequently genotyping by real-time PCR (AnyplexTM II HPV28 Detection, Seegene).

Results: Of the 1,177 samples genotyped, 420 (36.33%) showed some type of inadequacy in the collection process and only 22 (1.89%) of all samples were considered invalid to HPV genotyping. The most common inadequacy considered were tube with changed color (300 samples; 71.4%), presence of feces (146 samples; 34.76%), followed by tube without liquid (12 samples; 2.86%). However, none of the inadequacies were significantly associated with the invalid genotyping condition.

Conclusions: Few samples were invalid to HPV genotyping and the presence of inadequacies in the samples does not impact on HPV genotyping. The results reinforce that HPV detection through anal self-sampling is a valuable strategy to screen patients at high risk for anal cancer.

FC09 - Vaccines 3

Tota Joseph
United States

Palmer Cody
United States

#3743

Forecast Reduction in RRP in the US Attributable to Quadrivalent and Nonavalent HPV Vaccination: A Dynamic Transmission Modeling Study

36 - Economics and modelling

Palmer C[1], Tota J[1]

[1]Merck, Westpoint, United states

Background/Objectives: Recurrent Respiratory Papillomatosis (RRP) is a rare life-threatening disease resulting from HPV infection in both children (Juvenile Onset RRP - JORRP) and adults (Adult Onset RRP - AORRP) with no cure. HPV infections that result in AORRP are generally contracted through sexual activity, while HPV infections in children are likely a result of vertical transmission through an infected mother. 95% of cases of RRP are thought to be caused by HPV types 6 and 11, which are both targeted by available quadrivalent (4vHPV) and nonavalent (9vHPV) vaccines. Using dynamic transmission disease modeling, we investigate how HPV vaccination has driven the observed decline of JORRP in the US, and the impact that it will have on future RRP incidence.

Methods: A dynamic transmission model for HPV infection and RRP disease was adapted to the US, utilizing pre-vaccination data on HPV prevalence and seroprevalence in US adults, birth cohort incidence of JORRP, age of diagnosis of JORRP, and incidence of AORRP. Rollout of 4vHPV and 9vHPV vaccination, accounting for known vaccine coverage rates since 2007, was simulated and projected forward. We also ran some counter-factual historical vaccination scenarios to investigate how vaccination in older adolescent age groups impacted JORRP decline. Finally, health economic results were collected, including costs-averted (2020 USD; discounted 3%) and QALYs gained compared to no vaccination.

Results: The model accurately reproduces the documented decline in JORRP among birth cohorts since 2007. Forecasting RRP incidence suggests that after 2030, we can expect to see 10 cases of JORRP per year or less among children under the age of 13. For AORRP, after 2040 virtually all new cases of AORRP are due to types not covered by the available vaccines. Averted treatment costs exceed 200 million USD over the time horizon, and QALYs gained were significant. We also show that 75% of the observed decline in incidence of JORRP since 2007 is due to vaccination of individuals aged 16 years and older.

Conclusions: Our modeling suggests that 4vHPV and 9vHPV vaccination has contributed to the documented decline of JORRP incidence by averting infection among adults and is providing protection for infants and children under 13 years of age. We have shown that vaccination of adults and older adolescents would be a key driver of rapid drops in RRP incidence in the early years of a national HPV vaccination program. Lastly, modeling suggests that, if current vaccination practice continues, after 2040 HPV6/11-related RRP will be eliminated, both among adults and children.

Doshi Mishelben
United States

Morais Edith
France

#3628

UNDERSTANDING HPV ORAL BURDEN AND 9-VALENT HPV VACCINE EFFICACY: DESIGN OF THE PROGRESS, BROADEN AND V503-049 STUDIES

29 - Oral HPV infection

Morais E[1], Tu Y[2]

[1]Center for Observational and Real-World Evidence, MSD, Lyon, France

[2]Merck , Kenilworth, United states

Background/Objectives: The burden of human papillomavirus (HPV)-related head and neck cancers (HNC) is high, and routine screening for early detection of these cancers is not available. As such, HPV vaccination represents an attractive approach to prevent HNC. Oropharyngeal cancer, the most studied HNC relative to HPV infection, disproportionately affects men. The proportion of other HNCs attributable to HPV remains unclear. Although countries have increasingly implemented gender-neutral HPV vaccination, globally male vaccination coverage remains low. To inform public health decisions and routine medical practice regarding vaccination of both genders, a better understanding of oral HPV natural history and the burden of HPV-related HNC is needed.

Methods: Three studies have recently been initiated to fill knowledge gaps related to the (1) overall burden of HPV-related HNC, (2) the natural history of oral HPV infection and associated risk factors, and (3) efficacy of HPV vaccination in preventing persistent oral HPV infection, a surrogate endpoint for HPV-related HNC. PROGRESS (The Prevalence of Oral HPV Infection, a Global Assessment) and BROADEN (Absolute Burden of HPV-Related Head and Neck Cancers) are two observational studies designed to assess oral HPV prevalence and natural history (i.e., incidence, persistence and clearance) and to estimate the fraction of oropharyngeal and non-oropharyngeal HNC cases attributable to HPV, respectively. These studies have been initiated in several countries using a common methodology. In addition, an international, double-blind, placebo-controlled trial (Protocol V503-049; NCT04199689) was initiated to evaluate efficacy of the 9-valent HPV vaccine against oral HPV persistent infection in adult men. While efficacy of HPV vaccines against anogenital persistent infection and disease endpoints has been well established, V503-049 is the first large randomized clinical trial to evaluate efficacy against persistent oral HPV infection.

Results: N/A

Conclusions: Data from BROADEN and PROGRESS will fill knowledge gaps concerning the natural history of oral HPV infection and burden of HPV-related HNC. Together with direct evidence of vaccine efficacy against persistent oral HPV infection from the randomized clinical trial, these data will aid physicians, patients and healthcare decision makers in understanding the potential impact of vaccination on reducing the overall burden of HNC.

Murphy Brendan
Canada

Brown Vivien
Canada

#3291

COLLABORATING TO SUPPORT GLOBAL ELIMINATION OF CERVICAL CANCER - THE "CANCER WON'T WAIT" PROGRAM IN CANADA

37 - Advocacy, acceptability and psychology

Palmay C[3], Murphy B[2], Mccarles J[2]

[1]University of Toronto, Toronto, Canada

[2]Merck Canada Inc, Kirkland QC Canada, Kirkland, Canada

[3]Private Practice, Toronto, Canada

Background/Objectives: Background: In 2018 the World Health Organization Called for the Global Elimination of Cervical Cancer (insert footnote) and invited organizations all over the world to join this movement. Feb 4th 2020 Canadian Partnership Against Cancer released the Canadian Action Plan (insert footnote). Federation of Medical Women of Canada (FMWC) approached Merck Canada Inc., Kirkland, QC, Canada to facilitate a collaboration between both organizations to increase awareness and create action to reduce/eliminate HPV related cancers in Canada. The result was the "Cancer Won't Wait" Movement. Objective: To raise awareness and encourage health care providers across all fields to become actively involved in helping Canada to achieve the CPAC goal of eliminating HPV related cancers.

Methods: Methods: FMWC and Merck Canada Inc., Kirkland, QC, Canada developed a collaboration agreement to identify roles and responsibilities. Merck Canada Inc., Kirkland, QC, Canada was responsible to use their field force to invite HCP's to join the "Cancer Won't Wait" movement and foster awareness and ongoing participation. FMWC and Scientific Experts were required to create newsletters highlighting Global, National and LOCAL initiatives that were being done to facilitate the WHO and CPAC objective.

Results: Results: In 2021 6 newsletters were created - all having a particular theme: 1) How to Pandemic Proof your Practice (identifying ways to keep vaccinating, and screening patients during COVID 2) From Local to Global (discussing Elimination initiatives across the world). 3) The Y Factor (We can not forget the males) 4) Vaccine Hesitancy and HPV (very timely with the role out of COVID vaccines) 5) Vaccination is a Team Sport (identifying the role that pharmacists can play). 6) Vaccines require collaboration (identifying the roles of schools, public health and HCP's). Despite all HCP's having COVID as a priority, 420+ HCP's have registered to join the movement with the intent of prioritizing HPV prevention within their practices. Cancer Won't Wait has been featured in the Canadian Pharmacist Journal(1), Immunize Canada Bulletin (2), and the Canadian Partnership Against Cancer(3).

Conclusions: Conclusion: The Cancer Won't Wait movement was a result of a public and private partnership. Continuing these types of collaborations will help the WHO, CPAC and other organizations achieve their Cervical Cancer Elimination Goals in their lifetime. This initiative will continue in 2022 and the goal is to reach 5000 HCP's . We encourage others to implement similar collaborations and initiatives.

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Wähner Cornelia
Germany

Wähner Cornelia
Germany

#3569

HPV VACCINATION UPTAKE IN BOYS AFTER INTRODUCTION OF GENDER-NEUTRAL HPV VACCINATION IN GERMANY INCLUDING IMPACT OF COVID-19 PANDEMIC - A RETROSPECTIVE DATABASE ANALYSIS

06 - HPV prophylactic vaccines

Wähner C[1], Hübner J[2], Meisel D[3], Schelling J[4], Zingel R[5], Wölle R[6], Mihm S[6], Reuschenbach M[7]

[1]Department of Medical Affairs, MSD Sharp , Munich, Germany
[2]Hauner'sches Children´s Hospital, Ludwig-Maximilians-University, Munich, Germany
[3]Gynecological practice Wettin, Wettin-löbejün, Germany
[4]Faculty of Medicine, Ludwig-Maximilians-University, Munich, Germany
[5]IQVIA Commercial GmbH , Frankfurt/main, Germany
[6]Department of Market Access, MSD Sharp , Munich, Germany
[7]Global Medical and Scientific Affairs, MSD Sharp , Munich, Germany

Background/Objectives: Since 2007 HPV vaccination in Germany has been recommended and funded for girls. In June 2018 a gender-neutral recommendation for adolescents 9-14 years (2 doses) with catch up to 17 years (3 doses) was published by the German Standing Committee on Vaccination (STIKO) and is part of mandatory funding since January 2019. Vaccination is provided by office-based physicians. The objective of this study was to monitor the uptake of HPV vaccination in boys in Germany. The data reported are an update with the most recent results, including impact of the COVID-19 pandemic.

Methods: Data were used from the IMS® Vaccine Analyzer database between January 2018 and August 2021. This database contains anonymized electronic medical vaccination records from a panel of office-based physicians (pediatricians, general practitioners, gynecologists) and was used for nation-wide projections of administered doses per month to vaccine-eligible adolescents of age 9-17 in Germany. Vaccine coverage rates for the eligible birth cohorts of the male population were estimated using German census data (DESTATIS).

Results: The number of boys (9-17 years) that received their first dose per month increased to the level in girls within four months after mandatory funding and reached a 2019 maximum of 53,139 in July. With the onset of the COVID-19 pandemic, a first drop in numbers for first doses in March 2020 was seen for boys and girls that however recovered quickly until May 2020 and numbers settled between around 33,000 and 55,000 until March 2021. Since April 2021 we have observed a continuous steep drop in administered doses per month with a minimum of 13,178 first doses for boys and 18,261 for girls in August 2021, corresponding to a reduction of 70.1% (for boys) and 50.0% (for girls) compared to the same month in 2019, respectively. Estimated vaccine coverage rates by the end of 2020 for 15- and 18 years old boys were 33.9% and 19.5%, respectively for the first doses and 16.9% and 7.6%, respectively for completed series.

Conclusions: The monthly uptake and annual coverage in boys strongly increased after mandatory funding in 2019 but vaccine coverage rates for boys were still low at the end of 2020. The numbers of administered doses of HPV vaccine decreased substantially among German adolescents during the COVID-19 pandemic, with largest impact in 2021 with a sharp drop by up to 70%. Due to the delay in data delivery, the most recent data is from August 2021 but the study is ongoing until December 2021 and updated results will be presented. To reverse the deficits on long-term health and economic consequences a sustained increase in HPV vaccination rates is required.

Milbourn Hannah
United Kingdom

Milbourn Hannah
United Kingdom

#3521

EVIDENCE OF CROSS PROTECTION FROM THE BIVALENT HPV VACCINE IN YOUNG FEMALES IN ENGLAND

03 - Epidemiology and natural history

[1]Blood Safety, Hepatitis, Sexually Transmitted Infections (STI) and HIV Division, UK Health Security Agency, London, United kingdom
[2]Virus Reference Department, UK Health Security Agency, London, United kingdom

Background/Objectives: In 2008 England introduced a human papillomavirus (HPV) vaccination programme using the bivalent vaccine (Cervarix®) protecting against HPV16 and HPV18, changing to the quadrivalent vaccine (Gardasil®) in 2012. We present type-specific HPV DNA results for non-vaccine types from young women undergoing chlamydia screening and women attending for cervical screening who were offered the bivalent vaccine.

Methods: Residual vulvovaginal swab (VVS) specimens were collected from 16-24-year-olds attending for opportunistic chlamydia screening between 2010-2018. Residual Liquid Based Cytology (LBC) samples were collected from cervical screening attendances, at age 25-29, as part of the National Health Service Cervical Screening Programme (NHSCSP), from 2016-2019. Anonymised specimens were sent to the UK Heath Security Agency's Virus Reference Department and underwent type-specific HPV DNA testing using an in-house multiplex PCR and Luminex®-based genotyping test. Analyses were restricted to women who would have been offered the bivalent, Cervarix, vaccine.

Results: 17,909 VVS specimens were collected from young women attending for chlamydia screening. The prevalence of HPV31, 33 and/or 45 infection, decreased between 2010-2018, from 6.5% to 3.1% (p value for trend <0.001) for 16-18 year olds and 8.6% to 2.8% (p value for trend <0.001) for 19-21 year olds. Prevalence of five high-risk (HR) HPV types (HPV31/33/45/52/58) declined from 19.9% to 7.3% (p value for trend <0.001) in 16-18 year olds and 21.6% to 9.1% (p value for trend <0.001) in 19-21 year olds. Significant declines were seen for each of these five types individually. 1,331 LBC samples were collected from women testing positive for any HR-HPV infection at cervical screening. Prevalence of HPV31/33/45 was slightly lower among individuals eligible for vaccination compared to those that were not eligible (20.2% (17.4 - 23.1) vs 24.8% (19.9 - 30.3)), but similar for the five HR-HPV types (45.1% (40.9 - 52.8) vs 46.8% (41.6 - 48.6)).

Conclusions: Following 10 years of high coverage vaccination, results from national surveillance of women eligible to receive the bivalent vaccine have shown declines in prevalence of HPV-16/18-related types (HPV31/33/45) and high risk types present in Gardasil 9 (HPV52/58), suggesting continuing evidence of cross-protection consistent with clinical trial evidence. Monitoring of changes in type-specific HPV prevalence is ongoing and remains relevant to inform and evaluate vaccine choice for this programme. Surveillance of type-specific HPV in cervical cancers is in progress - to provide the final evidence of cross-protection from the bivalent vaccine use in England.

Macdonald Iain
Ireland

Macdonald Iain
Ireland

#3319

RAISING HPV VACCINE AWARENESS AND ADVOCACY THROUGH STEAM WORKSHOPS

38 - Health education

Macdonald I[1], Healy C[1], Malone E[2], Firth R[2], Mcdermott A[1]

[1]Maynooth University, Maynooth, Ireland

[2]Edinburgh Napier University, Edinburgh, United kingdom

Background/Objectives: HPV Immunity Community seeks to find new ways to educate and improve Human Papilloma Virus (HPV) vaccination awareness and advocacy amongst school children. The project brought together Irish and Scottish academics from Design, Biology, and Education, and the Irish Cancer Society (ICS), in an interdisciplinary, intersectoral and international collaboration. Our aim was to improve students' understanding and awareness of, and advocacy for, vaccination, and counter misinformation, about the HPV vaccine. HPV vaccines can save lives and eradicate associated cancers, but the uptake of the vaccine among first-year second level schoolgirls in Ireland, to whom it is offered for free, has dropped from 87% in 2020 to 50% in the space of two years (ICS 2021). The focus and prioritisation of the recent COVID-19 vaccination roll-out has contributed to the reduced uptake.

Methods: A qualitative arts-based research methodology was adopted and embedded in a series of workshops, delivered consecutively, over one week. The innovative STEAM approach used drama in education activities, storytelling through artwork and video creation, and focus group interviews. The workshops facilitated a dialogue amongst the participants to co-create localised, culturally inclusive, and scientifically informed stories. Following ethical approval the study involved 16-17 year olds (n=20) from three Irish post-primary schools in County Kildare, Ireland. Using the principles of Storytelling the students developed concept boards, scripts and storyboards through an iterative process of presentations and idea selection in a visual thinking methodology (Avgerinou and Pettersson 2020). COVID restrictions forced a blended delivery with a mix of in-person and parallel online collaborative participation from colleagues in Scotland, and contributors from ICS. We evaluated the success and impact of our programme on 3 key criteria: their knowledge of immunology, their confidence in expressing their knowledge about immunology, and their confidence in advocating for vaccination and countering misinformation.

Results: Analysis of the data drew out 5 key insights: people no longer fear the serious diseases due to the success of the immunisation programmes, a lack of personal research and open discussion results in there being a poor awareness of HPV vaccine, a STEAM approach was successful at changing students' attitudes towards the HPV vaccine from passive to positive, combining creative methods with scientific concepts leads to meaningful change in human behaviour, HPV vaccine advocates were created through the use of a STEAM approach to health education.

Conclusions: The programme has empowered the young people involved to become advocates for HPV and other vaccines in their peer group and community and hence we might anticipate their health will benefit. More importantly the clear positive impact of the programme shows us that these methods hold the promise of being a template for how to positively impact the health trajectory of others across inter-generations within schools, families and as future parents. We are currently working with ICS to get wider attention and notice for our methods in the hope of greatly extending its reach and potential. As we do this we will educate and protect the participants from the cancers prevented by HPV vaccination and also help insulate these communities from the growing tide of health misinformation.

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Zakhirova Nargiza
Uzbekistan

Zakhirova Nargiza
Russia

#3257

NATIONAL HPV VACCINATION PROGRAM IN THE REPUBLIC OF UZBEKISTAN

06 - HPV prophylactic vaccines

Zakhirova N[1], Tillyashaykhov M[1], Akhmedov O[1], Osmanova E[1], Saydakhmedova V[1], Islamova Z[1], Mamatova M[1]

[1]Republican Cancer Center, Tashkent, Uzbekistan

Background/Objectives: Cervical cancer prevention by introducing HPV vaccination in the Republic of Uzbekistan.

Methods: According to the national immunization schedule, with the support of international organizations GAVI, WHO, UNICEF and the Ministry of Health of the Republic of Uzbekistan, the HPV vaccination program for 9-year old girls was launched in 2019. Used vaccine Gardasil MK (tetravalent) 2 doses 0-6 months. Vaccinations were carried out in medical offices of public and private schools, in family polyclinics at the place of residence.

Results: From October 2019 to June 2021, 2 rounds of HPV vaccinations were carried out. In the first round, 290585 girls out of 297018 were vaccinated throughout the Republic, vaccination coverage was 97.8%. In the second round, 300893 girls were vaccinated out of 304,390 to be vaccinated, vaccination coverage was 98.8%. In total, 591,478 girls of 9 years old were vaccinated with HPV in the republic. Adverse reactions to vaccination were observed in 68 (0.1%) girls in the form of subfebrile fever, no serious complications after vaccination were observed. In November of this year, it was begun the first round of vaccination of girls 12-14 years oldin the Republic.

Conclusions: In the Republic of Uzbekistan, the national HPV vaccination program for 9-year old girls was carried out successfully, with a total coverage of 98.3%.

FC12- HPV disease and Covid-19

Olthof Ellen
Netherlands

Olthof Ellen
Netherlands

#3688

THE IMPACT OF COVID-19 ON THE DUTCH CERVICAL CANCER SCREENING PROGRAMME

01 - HPV disease and COVID-19

De Kok I[1], Siebers A[2], Van Kemenade F[3], Aitken C[3]

[1]Erasmus MC University Medical Center Rotterdam, Department of Public Health, Rotterdam, Netherlands

[2]PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands, Houten, Netherlands

[3]Erasmus MC University Medical Center Rotterdam, Department of Pathology, Rotterdam, Netherlands

Background/Objectives: The COVID-19 pandemic has had a major impact on cancer screening programmes worldwide. The Dutch government decided to temporarily stop the cervical cancer screening programme in March 2020 by not sending new invitations, reminders or self-sampling kits to women. Following the end of the first lockdown in June 2020, there was a progressive resumption of the programme. Additional catch-up measures were taken in October-November to speed up invitations and participation, such as sending out 120% of the usual monthly invitations and offering more prominent self-sampling in the invitation letter. We aimed to investigate the effect of the COVID-19 measures on short term outcomes of the Dutch cervical screening programme, by comparing these with data from 2018 and 2019.

Methods: Data from the national information system for cervical cancer screening (ScreenIT, Topicus, Deventer, the Netherlands) and the nationwide network of cyto- and histopathology in the Netherlands (PALGA) were used for this study. Women eligible for screening in 2018, 2019 and 2020 were included. These three cohorts were compared using the following indicators: participation rate stratified by age, region and screening history; time between invitation and participation; type of screening test used (self- or clinician sampled); time between an hrHPV positive self-sampling result and reflex cytology; hrHPV positivity; cytology result and direct referral rates.

Results: In total, 297,076 women participated in the Dutch cervical screening programme in 2020. The participation rate in 2020 (49.8%) was lower than that of 2018 (57.6%) and 2019 (56.1%). The decrease in participation was partly caused by a low participation rate of women invited between January and March 2020. This group also participated later compared to previous years. The use of self-sampling was higher in 2020 (16.1% of all participants) compared to 2018 (6.7%) and 2019 (8.6%). This was observed in all age groups and screening regions. There were no clinically relevant differences observed for the other indicators.

Conclusions: The interruption of the Dutch screening programme due to COVID-19 had impacted women who were invited in the first three months of 2020 the most; these women had lower participation rates compared to women invited in the same months in 2018 and 2019. The broader offer of self-sampling that was introduced in November 2021 had clearly an effect on the number of women who have used self-sampling. It is recommended to send re-invitations to women who were invited between January and March 2020 and did not participate to ensure these women have sufficient opportunity to participate.

Parker Susan
United States

Montealegre Jane
United States

#3779

Influence of COVID-19 pandemic on participation in HPV self-testing trial

01 - HPV disease and COVID-19

Parker S[1], Daheri M[2], Benavides E[1], Kasbaum M[1], Escobar B[1], Chiao E[3], Schmeler K[3], Anderson M[6], Deshmukh A[4], Hilsenbeck S[1], Jibaja-weiss M[1], Bulsara S[1], Zare M[2,5], Scheurer M[1], Montealegre J[1]

[1]Baylor College of Medicine, Houston, United states

[2]Harris Health System, Houston, United states

[3]The University of Texas MD Anderson Cancer Center, Houston, United states

[4]UTHealth Science Center School of Public Health, Houston, United states

[5]UTHealth McGovern Medical School, Houston, United states

[6]University of South Florida, Tampa, United states

Background/Objectives: The COVID-19 pandemic led to health system restrictions and closures, leading to gaps in preventive care. To our knowledge, the relationship between the COVID-19 pandemic and use of HPV self-test kits has not been assessed among patients in a large urban safety net health system that provides services to predominantly racial/ethnic minority, medically underserved populations. We aimed to describe the influence of the COVID-19 pandemic on the use of mailed HPV self-test kits within a safety net health system.

Methods: We assessed the influence of the COVID-19 pandemic on the use of mailed HPV self-test kits as part of a randomized controlled trial to evaluate the effectiveness the kits. Participants are women, ages 30-65 years in an urban safety net healthcare system who are underscreened for cervical cancer. We conducted a telephone survey in English and Spanish among a subgroup of trial participants who were randomized to receive the at-home HPV self-test kits.

Results: Among the 124 women who have completed the survey to date, the majority are Hispanic (70.2%) and Black or African American (20.2%). Among the women surveyed, 78.1% reported using the kit to take a sample. Of those who used the kit, over half (58.5%) said that the COVID-19 pandemic influenced their decision to use the kit. When asked in what way the pandemic influenced their decision, most of the open-ended responses fell into three categories: (1) women felt safer collecting their sample at home for fear of being exposed to COVID, (2) their clinic was closed due to shut-down measures or they had difficulty getting an appointment, and (3) they felt more comfortable/less embarrassed collecting their sample at home. The majority of women who used the kit (87.7%) said the kit was easy to use and almost all (96.3%) stated they would be willing to use an HPV self-sample kit again.

Conclusions: Preliminary results from our survey suggest that the COVID-19 pandemic influenced women an urban safety-net healthcare system to participate in an at-home HPV self-test trial. Overall, the kit had high acceptability among trial participants.

Kepka Deanna
United States

Kepka Deanna
United States

#3777

Intention to receive COVID-19 vaccination relates to HPV vaccination receipt among young adults ages 18-26 years in the western region of the United States

40 - Public health

Christini K[2], Mann S[1], Chang E[1], Lipscomb J[1,2], Kepka D[1,2]

[1]University of Utah, Salt lake city, United states

[2]Huntsman Cancer Institute , Salt lake city, United states

Background/Objectives: To assess similarities and differences between receipt of the HPV vaccine and intention to receive the COVID-19 vaccine among young adults by demographic factors in the western region of the United States.

Methods: An online, self-administered, cross-sectional survey was conducted from October 2020 to April 2021 that included young adults ages 18-26 years old who live in rural and urban communities in the western region of them United States. Participants were recruited through university, public health, and community list servs (N=2889). The questionnaire asked participants to provide information on their demographics; general levels of trust in vaccinations; HPV and HPV vaccination knowledge, trust in HPV vaccine effectiveness, and receipt of the HPV vaccine. The questionnaire also included COVID-19 questions related to COVID-19 testing, COVID-19 concerns, and COVID-19 vaccination intentions. We hypothesized that a difference in COVID-19 vaccination intention between those who had received an HPV vaccination or not would be found, expecting the decision-making process for getting the HPV vaccine and the COVID-19 vaccine to be similar. HPV vaccination was self-reported. Chi-square and penalized binary multivariate logistic regression were utilized.

Results: After controlling for the effect of gender, age, race and ethnicity, health insurance, frequency of religious services, and rurality, the odds of young adults who had received any HPV vaccination stating that they intended to get COVID-19 vaccinated was 1.58 (95%CI: 1.33-1.88) times higher than those who had not had any doses of the HPV vaccine. After model adjustments, being male (1.41, [1.16 - 1.72]), identifying as non-Hispanic racial minority (1.33, [1.03 - 1.72]), having health insurance (0.49, [0.39 - 0.61]), and living in rural areas (0.50, [0.41 - 0.59]) all had significantly different odds of COVID-19 vaccination intent. Rural young adults stated, at significantly higher frequencies, that they would be unlikely to receive the COVID-19 vaccine, even if recommended by their health care provider, than did urban young adults (24% vs 7%, $P<0.001$).

Conclusions: Our research indicates that the decision-making process of intent to receive COVID-19 vaccination among young adults and that of receiving HPV vaccination are similar, and that the presence of any HPV vaccination may be a strong predictor of intent to vaccinate against COVID-19 infection among young adults. Targeted interventions are needed to address both HPV vaccine hesitancy and COVID-19 vaccine hesitancy to improve vaccination rates. Rural communities in the western United States would benefit greatly from interventions that address HPV and COVID-19 vaccine hesitancy among young adults.

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Olkov Ilya
Russia

Olkov Ilya
Russia

#3653

REALIZATION OF WHO GLOBAL STRATEGY ON CERVICAL CANCER ELIMINATION IN RUSSIA IN COVID-19 ERA

01 - HPV disease and COVID-19

Olkov I[1], Kononova I[2]

[1]Social Programs Development Foundation , Moscow, Russia

[2]Chair of obstetrics and gynecology, Russian Pirogov National Medical Research University , Moscow, Russia

Background/Objectives: To analyze the implementation of WHO Global Strategy on Elimination of Cervical Cancer in Russia during COVID-19 era.

Methods: Analysis of the HPV screening implementation, vaccination against HPV and treatment of patients with SIL was performed. To determine the adherence of the population to screening and vaccination a sociological study of 2900 medical workers and 236 590 women from various regions of Russia was carried out. To determine efficacy of HPV screening implementation 5 pilot regional screening programs were initiated in Russia for a cohort of 60 000 women at 30-49 years.

Results: Various screening techniques have been introduced in Russian regions: in remote areas PAP test is performed as part of a clinical examination of the population once every 3 years with detection of up to 22% of CIN and cervical cancer. In large cities and megalopolises of a number of regions, active HPV screening by HC2 is being introduced with detection of up to 75% of CIN and cervical cancer. 60 000 women from 30 to 49 years were enrolled into the screening program and 98,68% were tested. HPV High Risk positive and PAP positive women were referred for colposcopy. In this group 32,7% were diagnosed with various CIN grades and duly treated. The widespread introduction of modern screening technologies is prevented by limited resources during COVID-19 pandemic. Regional vaccination against HPV is being increased too, although lack of HPV vaccination in National Immunization Schedule remains critical. To facilitate implementation of the Global Screening Strategy, a unique model for the formation of professional competencies in training programs was developed, including visualization, virtualization, CIN treatment simulation environments, information management and CASE decision-making system, which increased competences of medical personnel by 12.5 times. Educational programs for the population included the use of innovative technologies for interactive discussion of HPV-associated diseases, enabled to carry out planned vaccination of 90 - 93% of children.

Conclusions: Implementation of WHO Global Strategy on Elimination of Cervical Cancer in Russia is being accelerated due to enthusiasm and determination of a number of medical activists, however, some problems remain and need to be addressed even in spite of a COVID-19 pandemic. We also faced some difficulties in the reaching of women enrolled into HPV screening regional programs during COVID-19 era. To overcome this, a complex informational and educational campaign was carried out both for local gynaecologists and local women with the help of local authorities, volunteers, mass media and new digital technologies.

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Tan Jerry
Australia

Chen Fei

#3676

PRELIMINARY PROOF AND SUGGESTION FROM THE CLINICAL DATA OF MULTICENTER RESEARCH ON THE APPLICATION OF REAL-TIME OPTOELECTRONIC DEVICE FOR CERVICAL CANCER SCREENING: IN THE REPEATED SURGES OF COVID-19 EPIDEMICS

22 - Artificial Intelligence

[1]1. Peking Union Medical College Hospital Chinese Academy of Medical Science, Beijing, China
[2]Beijing Chaoyang Hospital of Capital Medical University, Beijing, China
[3]Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China
[4]4. Peking University Third Hospital, Beijing, China
[5]5. Xiangya Hospital of Central South University, Changsha, China

Background/Objectives: The main purpose of this study is to verify the feasibility of real-time optoelectronic device (TruScreen; TS) for cervical cancer screening based on the data of five hospitals, especially during the repeated surges of COVID-19 epidemics.

Methods: The participating hospitals in this study were divided into training set (n = 5) and test set (n = 64). A total of 17447 participants were included in the study and tested by cytology, HPV, TS and gynecological examination from September, 2018 to June, 2021. When each test is positive result, the patient will go forward to colposcopy. The informed consent forms were signed by all participants. The inclusion criteria were female patients older than 20 years with sexual activity. Patients who had acute infections in the lower genital tract, pregnant or undergoing treatment of the cervix were excluded.

Results: Participants in both training set and testing set have completed case collection and all tests. 1,022 women data of the training set were analyzed in the study. 62.4% of the women were cytological ASC-US+, 91.3% were high-risk HPV positive. TS test was abnormal in 41.5% women. 261 women were diagnosed as CIN2+ lesions. The highest risk of CIN2+ was 0.61 for women with HPV 16/18+ and abnormal TS results. For detection of CIN2+, the sensitivity and specificity for TS was 90.4% and 75.3%, and sensitivity was statistically higher than cytology (82.4%). The specificity of cytology and hrHPV DNA testing were significantly lower than that of TS ($P<0.001$). Participants in the test set have completed case collection and all tests.

Conclusions: TS has the advantages of good sensitivity, specificity, objectivity and real-time. It is a noninvasive, simple and rapid method for the diagnosis of cervical lesions. TS is particularly suitable as primary screening method for cervical cancer that women and medical staff facing SARS-CoV-2 exposure and infection risks in hospital during the repeated surges of COVID-19 epidemics.

Hillen Christoph
Germany

Hillen Christoph
Germany

#3593

PREVALENCE OF GENITAL HPV INFECTIONS AMONG FEMALE TRANSPLANT RECIPIENTS

01 - HPV disease and COVID-19

Hillen C[1,1], Sachs C[1,1], Jaeger A[1,1], Prieske K[4], Kaufmann A[5], Lütgehetmann M[6], Schmalfeldt B[1,1], Sterneck M[8], Woelber L[9]

[1]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[3]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4]Dysplasia Center Hamburg at Jerusalem Hospital, Hamburg, Germany

[5]Clinic for Gynecology, Charité – Berlin Institute of Health, Charite – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

[6]Hygiene Institute for Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, Hamburg, Germany

[7]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[8]Department of Medicine and University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[9]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf; Dysplasiezentrum Hamburg, Jerusalem Hospital, Hamburg, Germany

Background/Objectives: Immunosuppressive therapy in organ transplant recipients is associated with a higher risk of developing anogenital (pre)malignancies related to Human Papillomavirus (HPV) infections. Previous studies on high-risk (hr) HPV prevalence among female transplant recipients have been inconsistent. Larger studies with accurate patient assessment are needed to assess hrHPV prevalence.

Methods: Female kidney or liver transplant recipients were HPV tested at the uterine cervix with Cobas® HPV Test (Roche Diagnostics) after at least one year of treatment. Further genotyping was performed by AnyplexTM II HPV28 (Seegene). All participants completed a questionnaire regarding medication, sexual behavior, transplant-related and medical history.

Results: 201 patients (median age 52; range 18-78 years) were included. 98 women had received a kidney transplant, 93 women a liver transplant, and 10 women simultaneously liver and kidney transplants. The median duration of immunosuppressive therapy was 9 years. 186/201 (93%) women had attended cervical cancer screening by PAP smear at least once a year before inclusion in the study and 25/201 (12.4%) were HPV vaccinated. To date, 144 cervical smears have been evaluated and 57 cervical smears and anal HPV test results will be available at data presentation. In 14.6% (21/144) of evaluated participants, the cervical HPV test was positive. HPV prevalence was 16.7% (12/72) in kidney and 12.5% (8/64) in liver transplant recipients. The most frequently detected genotype was HPV16 (43%). HPV positively tested women had an average of 6-lifetime sexual partners compared to 3 in HPV negative patients (p=0.013). 20/21 patients participated in the follow-up. Cervical hrHPV infection was confirmed in 17/20 (85%) patients, and 11/17 had anal hrHPV co-infection. Biopsies were obtained in 10/21 patients and three patients were confirmed to have high-grade dysplasia (1x cervical intraepithelial neoplasia (CIN) II, 1x CIN III, 1x vaginal intraepithelial neoplasia III).

Conclusions: Data indicate that the prevalence of cervical hrHPV in female transplant recipients is more than twice of that of the general population (6,2% in women above 30 years (Luyten et al., 2014)). Most women (93%) participate in regular cervical cancer screening, however, additional colposcopy might be beneficial to screen for (pre)invasive lesions of portio, vulva and vagina in HPV+ transplant recipients. Final results including anal swab will be available for a presentation showing hrHPV prevalence in the transplant group and the rate of anal co-infection.

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Felsher Marisa
United States

Morais Edith

#3453

THE IMPACT OF COVID-19 ON THE IMPLEMENTATION OF PROGRESS (PRevalence of Oral hpv infection, a Global aSSessment) STUDY

29 - Oral HPV infection

[1]Merck , Kenilworth, United states
[2]MSD, Lyon, France
[3]IQVIA, barcelona, Spain
[4]Hopital Europeen Georges-Pompidou, Paris, France
[5]Cancer Epidemiology Research Program, Catalan Institute of Oncology - IDIBELL, Hospitalet de Llobregat; and CIBERESP, Granvia de l'Hospitale, Barcelona, Spain
[6]German Cancer Research Center (DKFZ), Heidelberg, Germany
[7]Center for Immunization and Infection Research in Cancer, Moffitt Cancer Center and Research Institute, Tampa, United states
[8]University of Florida College of Dentistry, St. petersburg, United states
[9]Rutgers Health University Dental Associates, New brunswick, United states
[10]Hospitales Universitarios San Roque, Las palmas, Spain
[11]Assistance Publique Hopitaux de Paris, Paris, France
[12]Institute of Head , Birmingham, United kingdom

Background/Objectives: Little is known about the natural history of oral HPV in the general population. We designed PROGRESS (PRevalence of Oral hpv infection, a Global aSSessment), a noninterventional study among adults recruited from dental offices in France, Germany, Spain, the United Kingdom and the United States (US) to assess oral HPV prevalence, incidence and persistence. The COVID-19 pandemic has impacted research conducted by dentists as the nature of their work puts them and patients at high risk of COVID-19 infection. We piloted PROGRESS in four dental sites to assess feasibility of study implementation during the global pandemic.

Methods: Between November 2020 and June 2021, four sites were selected for the pilot phase: one in France, one in Spain and two in the US. Participating dentists were instructed to recruit 68 patients presenting for dental examinations over a minimum of 28 and maximum of 40 working days, for 272 participants total. The study was approved by Ethics Committees in accordance with local and national requirements. Participants gave informed consent, completed questionnaires and provided oral rinse/gargle (ORG) specimens. ORG specimens were shipped to reference laboratories for HPV-DNA detection using the SPF10/DEIA/LiPA25 system. Implementation was assessed as follows: total participants enrolled per site; total days between first and last participant in study per site; total ORG samples transported to laboratory; proportion of samples adequate for testing; and total completed participant questionnaires. Interviews were held with dentists to identify hurdles to study implementation.

Results: Three dentists recruited 68/68 participants; the French site recruited 45/68 participants for a total of 249 participants. The mean number of days between first and last participant enrolled was 60 days: 65 days in France, 66 days in Spain, 28 days in US site 1 and 82 days in US site 2. There were 249/249 samples collected and sent to reference laboratories, 249/249 samples processed and classified as adequate after DNA quality control and 249/249 completed questionnaires. Dentists reported that recruitment delays were due to insufficient time and staff to execute fieldwork.

Conclusions: COVID-19 did not impact ORG collection, transportation, or processing nor completion of questionnaires, but did impact the rate at which participants were enrolled in three of four sites, due to insufficient time and staffing. PROGRESS will expand to 108 more dental sites and enroll 7,628 participants between 2021 and 2022. Strategies to support rapid participant recruitment such as weekly reminder calls will be used to ensure timely enrollment.

FC14- Self-sampling 1

Hendrickx Jhana
Belgium

Hendrickx Jhana O.
Belgium

#3725

FIRST-VOID URINE: A RELIABLE APPROACH FOR CERVICAL CANCER SCREENING

10 - HPV screening

Hendrickx J[1], Jordaens S[1], Meers N[1], Rios Cortes A[1], Pasmans D[1], Beyers K[1], Vankerckhoven V[1]

[1]Novosanis NV, Wijnegem, Belgium

Background/Objectives: A global analysis of cervical cancer (CC) incidence and mortality in 2018 revealed 570 000 cases of cervical cancer and 311 000 deaths from the disease, making it the fourth most common cancer in the world.1,2 CC is primarily caused by infections with high-risk strains of the human papillomavirus (hrHPV). The golden standard to test for hrHPV infections is a physician taken smear (PTS). However, this screening method has a suboptimal attendance rate due to reluctance, discomfort and cultural barriers. The Colli-Pee® device by Novosanis is user-friendly allowing for the collection and stabilization of first-void (FV) urine to enable self-sampling for the purpose of HPV screening. The aim of this abstract is to provide consolidated data on the clinical performance of the Colli-Pee® device compared to PTS from several studies that explored the detection of HPV in self-samples.

Methods: Novosanis developed the Colli-Pee® portfolio for standardized and volumetric (10mL, 20mL) self-sampling (SS) of FV urine. Additionally, Colli-Pee® can be prefilled with Novosanis' UCM, to allow preservation and stabilization of HPV DNA in urine. Colli-Pee® containing UCM is CE-IVD marked, and has been registered in several countries worldwide. In total, eight clinical trials have been reviewed to assess the potential of Colli-Pee® -collected FV urine compared to PTS and different vaginal SS devices for the detection of HPV.

Results: A total of 2443 women were enrolled and consented their participation in the trials. Seventeen different institutions are involved covering multiple European regions and the state of New Jersey, USA. Overall, 9 different HPV assays were used to investigate the clinical performance of Colli-Pee® against a PTS and nine different vaginal SS devices. Throughout, high overall HPV positivity was detected with Colli-Pee® collected FV urine on high-throughput HPV assays and the concordance for hrHPV detection between FV urine and cervical samples ranged from good to very good.

Conclusions: The clinical performance of FV urine for hrHPV detection is non inferior to that PTS as tested via multiple HPV high-throughput assays. Thus, FV urine can be considered an appropriate and user-friendly sample type for CC screening that can improve attendance rates because it is painless, can be used in a home setting, and does not create cultural barriers making it easier to target hard-to-reach and under-screened populations. Furthermore, new generation of Colli-Pee® devices are being evaluated in the framework of the CASUS study for the collection and stabilization of smaller volumes and the compatibility of collection tubes with high-throughput machines in favor of CC screening.

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Van Keer Severien
Belgium

#3524

CLINICAL EVALUATION OF HPV-DNA TESTING IN HOME-COLLECTED FIRST-VOID URINE COMPARED TO PAIRED CERVICAL SAMPLES: UPDATE ON VALHUDES

13 - Self-sampling

Van Keer S[1], Latsuzbaia A[2], Vanden Broeck D[3], De Sutter P[4], Donders G[5], Doyen J[6], Tjalma W[7], Weyers S[8], Van Den Borst E[9]

[1]Centre for the Evaluation of Vaccination (CEV), Vaccine , Wilrijk (antwerp), Belgium

[2]Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium

[3]Laboratory of Molecular Pathology, AML Sonic Healthcare, Antwerp, Belgium

[4]Department Gynaecology-Oncology, UZ Brussel – VUB, Brussels, Belgium

[5]Department of Obstetrics and Gynaecology of the General Regional Hospital Heilig Hart, Tienen, Tienen, Belgium

[6]Department Gynaecology-Obstetrics, University Hospital Liège, Liège, Belgium

[7]Multidisciplinary Breast Clinic, Unit Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Antwerp University Hospital (UZA), Antwerp, Belgium

[8]Department of Obstetrics and Gynaecology, Ghent University Hospital, Ghent, Belgium

[9]Human Molecular Genetics, Centre of Medical Genetics (CMG), Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Edegem (antwerp), Belgium

Background/Objectives: Urine collection is a non-invasive self-sampling method offering new perspectives in light of reaching women un(der)-screened for cervical cancer. Little evidence is available regarding the clinical accuracy for high-risk (hr)HPV testing on urine. VALHUDES was designed as a diagnostic test accuracy study aiming to compare the clinical accuracy to detect cervical intraepithelial neoplasia grade two or worse (CIN2+) of HPV assays on self-collected samples, including first-void (FV) urine, compared to HPV testing on paired clinician-collected cervical samples.

Methods: 523 women attending colposcopy due to a previous abnormal screen test were enrolled at five Belgian colposcopy clinics (NCT03064087). Women collected a FV urine sample (Colli-Pee with Urine Conservation Medium; Novosanis) at home the day before colposcopy. A cervical sample was taken by a gynaecologist prior to colposcopy (Cervex-Brush, Rovers in Hologic PreservCyt Solution). Disease outcome was assessed by colposcopy and histological assessment of biopsies if indicated. FV urine (index test) outcomes were available for Abbott Alinity m HR HPV (n=494), Roche Cobas 4800 (n=485), and Roche Cobas 6800 (n=491) with paired results using the same HPV test on the cervical samples (comparator). Manufacturer's instructions including assay cut-offs used for cervical samples were applied for FV urine as well. Differences in accuracy were assessed by relative sensitivity and specificity (FV urine vs cervical) with McNemar 95% CI.

Results: Paired samples were available from women aged 19 to 72 years (median age 40). HrHPV testing in FV urine with Abbott Alinity m HR HPV was similarly sensitive for CIN2+ (ratio 0.92; 95% CI: 0.84-1.02) and specific (ratio 1.03; 95% CI: 0.95-1.11) compared to testing cervical samples. Likewise, similar clinical accuracy was found in FV urine compared to cervical samples using both Roche Cobas 4800 (ratio [sensitivity for CIN2+] 0.98; 95% CI: 0.93-1.02, ratio [specificity <CIN2] 0.99; 95% CI: 0.91-1.09) and Roche Cobas 6800 (ratio [sensitivity for CIN2+] 0.96; 95% CI: 0.91-1.02, ratio [specificity <CIN2] 1.01; 95% CI: 0.93-1.09).

Conclusions: These results demonstrate that HPV-DNA based PCR testing is similarly sensitive (CIN2+) and specific (<CIN2) on home-collected FV urine compared to HPV testing on paired cervical specimens taken by a clinician. In agreement with previous clinical evaluations of validated HPV-DNA based PCR tests within VALHUDES, this offers new perspectives in light of reaching un(der)-screened women in organized cervical screening programs. As now, FV urine sampling is not only well-accepted by women, but has a proven similar clinical accuracy compared to cervical samples too using high-throughput HPV-DNA based PCR assays used in routine cervical screening.

Beyers Koen
Belgium

Beyers Koen
Belgium

#3660

EXPLORATIVE STUDY ON DEVICE ARCHITECTURES FOR DEFINED RANGES OF FIRST-VOID URINE COLLECTION

13 - Self-sampling

Beyers K[1], Ríos Cortés A[1], Jordaens S[1], Meers N[1], Hendrickx J[1], Pasmans D[1], Tijsen J[1], Vankerckhoven V[1]

[1]Novosanis NV, Wijnegem, Belgium

Background/Objectives: A properly collected first-void urine (FVU) sample is important for accurate detection of e.g. sexually transmitted infections, human papilloma virus or cancer biomarkers. FVU contains a higher number of specific analytes, improving diagnostic accuracy. For this reason, Novosanis developed Colli-Pee®, a user-friendly FVU self-collection device. Moreover, Novosanis expanded its Colli-Pee® portfolio with specific collection tubes in different sizes and volumetric capacities (e.g. 20mL and 10mL) compatible with diagnostic carriers. The aim of this study was to explore the capability of the different Colli-Pee® variants to collect small, regular and large volumes, while maintaining the quality of the FVU sample and respecting the urine-to-preservative ratio.

Methods: Scaling of device architectures in combination with known limitations of injection molding techniques, requires complex miniaturization efforts while tackling unscalable laws of hydrodynamics, allowing for ranges of collected FVU from e.g. 4mL up to 40mL. Development items we segregated in: (i) a device platform that allows push-fit or threaded tube connection in different sizes with Colli-Pee®, (ii) an inlet funnel capable of processing a urine flow of up to 25mL/s, (iii) selection of hydrophobic polymers for clean sample collection, without loss of materials sticking to inner sidewalls, (iv) an inflow duct to access the collection tube, (v) immediate mixing with preservative , (vi) a floater with an air pocket, with sufficient buoyancy for lifting the valve assembly, (vii) a valve on top of the floater that closes access to the tube when a specific range of FVU has filled the tube, (viii) and the same valve that opens pass through flow of midstream urine though the device's outlet into the toilet, Banking on 2 patents, a number of conceptual designs, simulation models, 3D CAD drawings and prints, the final Colli-Pee® designs were manufactured in injection molded parts.

Results: The resulting differences in physical design between the volumetric variants showed similar performance with regard to FVU sample quality and relative collected range, guaranteeing proper sample stabilization with prefilled chemistry volumes. All designs proved to be well-suited for upscaling and mass manufacturing, with good sample stability, allowing additional clinical evidence to be acquired.

Conclusions: Currently, Colli-Pee® variants collecting small volumes (approx. 10mL, CE-IVD or approx. 4mL, RUO), regular volumes (approx. 20mL, CE-IVD), and large volumes (approx. 40mL, RUO) are available and performing well. These variants give customers and users the possibilities to tailor fit their diagnostic solution with analyte concentrations, high-throughput carriers, and home-based postal solutions.

Berza Natalija
Latvia

Berza Natalija
Latvia

#3637

Acceptability of HPV self-sampling test in a population of Latvian women (preliminary data)

13 - Self-sampling

Zodzika J[1,2]

[1]Riga Stradiņš University, Riga, Latvia

[2]Riga Eastern Clinical University Hospital, Riga, Latvia

Background/Objectives: Participation in cervical cancer screening is the cornerstone of cervical cancer detection. Latvia has a low attendance rate for cervical cancer screening and a relatively high incidence of cervical cancer. HPV self-sampling is an alternative strategy to improve cervical cancer screening program compliance. The study aims to evaluate the acceptability of self-sampling for human papillomavirus (HPV) testing in the population of Latvian women.

Methods: From February till October 2021women who attended the colposcopy unit in Riga Eastern Clinical University Hospital for known cervical pathology were invited to participate in the study. They were asked to perform unsupervised HPV self-sampling using written instructions, and after the procedure was asked to fill in the questionnaire regarding the course and admissibility of the procedure. The study was approved by the Ethics Committee of Riga Stradiņš University.

Results: A total of 262 women were invited to participate in the study. 237 (90.5 %) participants agreed to provide a self-sample; of them, 93 (35.5 %) women found self-sampling acceptable and equivalent to the clinician-administered test. 134 (51.1 %) of patients reported that they would like to have a test carried out by a medical professional next time. Nineteen females (7.3 %) graded their feelings during the self-sampling test as "'embarrassed during the procedure" or "'strongly embarrassed during the procedure". 37 (14.1%) participants recorded mild or severe discomfort during the procedure. On the other hand, 36 (13.7 %) patients felt strong self-confidence during self-sampling, and 20 (7.6%) participants were interested or intensely interested in taking the test.

Conclusions: Self-sampling for HPV testing was acceptable in many patients, and women could carry out the test alone, using simple written instructions. The main arguments against performing self-sampling were shame regarding this procedure and discomfort during the procedure. This issue will need to be addressed if self-sampling is introduced.

References:

Nitkowski Jenna
United States

Nitkowski Jenna
United States

#3470

EFFECTS OF ENVIRONMENTAL CONDITIONS ON HOME-BASED SELF-SAMPLING KITS FOR ANAL CANCER SCREENING

13 - Self-sampling

Nitkowski J[1], Giuliano A[2], Ridolfi T[3], Chiao E[4], Fernandez M[5], Schick V[6], Swartz M[7], Smith J[8], Brzezinski B[1], Nyitray A[1]

[1]Medical College of Wisconsin, Center for AIDS Intervention Research, Milwaukee, United states

[2]Moffitt Cancer Center and Research Institute, Center for Immunization and Infection Research in Cancer, Tampa, United states

[3]Medical College of Wisconsin, Cancer Center, Milwaukee, United states

[4]The University of Texas, MD Anderson Cancer Center, Houston, United states

[5]The University of Texas Health Science Center at Houston School of Public Health, Department of Health Promotion and Behavioral Sciences, Houston, United states

[6]The University of Texas Health Science Center at Houston School of Public Health, Department of Management, Policy and Community Health, Houston, United states

[7]The University of Texas Health Science Center at Houston School of Public Health, Department of Biostatistics and Data Science, Houston, United states

[8]University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel hill, United states

Background/Objectives: The performance of home-based self-sampling kits may be subject to environmental conditions such as extreme temperatures, freeze thaw cycles, or long transport times in transit to laboratories. We aim to determine the environment's effect on specimen adequacy for HPV genotyping of a home-based self-sampling anal cancer screening kit.

Methods: The Prevent Anal Cancer Study in Milwaukee, Wisconsin, USA recruited men who have sex with men and transgender persons 25 years of age or older. One-half of participants were randomized to receive a mailed self-collection kit which included a flocked swab (Copan Italia Spa), a vial of 2 mL of standard transport media (Qiagen), and a temperature recorder. The kits were insulated with foam and temperature was recorded every twenty minutes. Participants mailed the kit back to the lab. Subsequently, the SPF10 LiPA assay was used for HPV genotyping including the detection of human ß-globin to determine sample inadequacy by qPCR. Using logistic regression, we assessed the association between specimen inadequacy and mean temperature, lowest temperature, highest temperature, temperature range, presence of a freeze-thaw cycle, and the number of days in an uncontrolled environment. This analysis assessed inadequacy for the first 52 kits.

Results: A total of 9.6% of specimens were inadequate for HPV genotyping. Kits experienced an average of 12.7 days in an uncontrolled environment at a mean temperature of 20.2°C. Kits were subjected to low temperatures ranging from -16.0°C to 21.4°C, and high temperatures ranging from 22.1°C to 39.4°C. On average, kits were subjected to a temperature range of 18.1°C (min=6.1, max=40.2). After adjusting for number of days in an uncontrolled environment, none of the time and temperature variables were associated with specimen inadequacy including low temperature (aOR 0.92, 95% CI 0.82-1.02), high temperature (aOR 0.95, 95% CI 0.72-1.24), and temperature range (aOR 1.12, 95% CI 0.98-1.27). A higher proportion of inadequate specimens experienced a freeze-thaw cycle (40%) as compared to adequate specimens (13%), but this difference did not reach statistical significance. Sensitivity analyses using participant-reported date of swabbing revealed that low temperature and temperature range were significantly associated with specimen inadequacy, although more of these data were missing and subject to recall bias.

Conclusions: Over 90% of home-based self-swabs were adequate. Despite transit during different seasons in Milwaukee, specimen inadequacy was not associated with temperature (low, high, mean, or range), freeze-thaw cycle, or days in an uncontrolled environment.

Iacobone Anna Daniela
Italy
Iacobone Anna Daniela
Italy

#3762

VALIDATION OF THE HPV ONCOPREDICT® ASSAY ON SELF-COLLECTED VAGINAL AND URINE SAMPLES: PRELIMINARY ITALIAN DATA OF THE EUROPEAN-VALHUDES STUDY.

13 - Self-sampling

Iacobone A[1,2], Bottari F[2,4], Preti E[1], Guerrieri M[1], Martella S[1], Giubbi C[3], Cocuzza C[3], Latsuzbaia A[5]

[1]European Institute of Oncology, Preventive Gynaecology Unit, Milan, Italy
[2]University of Sassari, Department of Biomedical Sciences, Sassari, Italy
[3]University of Milano-Bicocca, Department of Medicine and Surgery, Monza, Italy
[4]European Institute of Oncology, Division of Laboratory Medicine, Milan, Italy
[5]Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium

Background/Objectives: HPV testing of minimally invasive self-collected samples represents a promising strategy to improve cervical cancer screening. The aim of the present study is to evaluate the performance of the HPV OncoPredict® assay, a double step reflex test consisting of an initial screening for HR-HPV E6/E7 sequences and a second quantitative assessment of normalized type-specific viral loads, on self-collected vaginal and urine samples as compared to clinician-taken cervical samples, according to VALHUDES (VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples) protocol [1].

Methods: Women aged 25-64 years referred to colposcopy at the European Institute of Oncology, Milan, were enrolled after giving informed consent. Prior to colposcopy, first-void urine and vaginal self-samples were taken with the ColliPee (Novosanis) and the FLOQSwab (Copan) collection devices, respectively. Physician collected cervical samples with the Cervex-Brush (Rovers Medical Devices). Colposcopy was performed with targeted biopsy if required. All samples were tested with the HPV OncoPredict® QT assay (Hiantis), a recently developed PCR-based test evaluated as part of WHO HPV Labnet international proficiency study [2].

Results: Overall, 288 samples were collected from 96 women. Forty-two out of 96 patients received colposcopy-targeted biopsy and histology report was CIN2+ in 60% (25/42) of cases. Sample host cell cellularity was similar in physician- and self-collected samples. Mean Log10 (copies CCR5/rx) was 3.840, 3.938 and 3.820 in cervical, vaginal and urine samples, respectively. The hrHPV test result concordance with cervical sample was 83.3% (80/96) for first-void urine and 82.3% (79/96) for vaginal samples. The most prevalent genotypes were HPV 16 and 31. Viral load was higher in cervical samples than self-collected samples; but it varied according to detected genotype. Interestingly, in nine HPV16-related CIN2+ mean viral load was 3.183, 3.407 and 2.748 Log10 (copies HPV16/rx) in cervical, vaginal and urine samples, respectively; whereas it was 3.870, 3.851 and 3.409 Log10 (copies HPV31/rx) in cervical, vaginal and urine samples of five women affected by HPV31-related CIN2+.

Conclusions: Preliminary data indicate a good overall agreement between HPV OncoPredict® assay results from self-collected and cervical samples. Furthermore, HPV genotyping and viral load may be useful as potential biomarkers in the triage of women with a hrHPV-positive self-sample. Acknowledgments: HPV OncoPredict® assays were developed as part of a European Commission funded SME Instrument Phase 2 Project (Grant agreement ID: 806551).

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Sørbye Sveinung
Norway

Aranda Flores Carlos Eduardo
Mexico

#3618

SELF- VERSUS CLINICIAN-COLLECTED SAMPLES FOR THE DETECTION OF HPV BY 14-type DNA AND 7-TYPE mRNA TESTS

13 - Self-sampling

Aranda Flores C[1], Sorbye S[2]

[1]Oncology Department, Hospital General de México "Eduardo Liceaga", Mexico city, Mexico

[2]University Hospital of North Norway, Tromso, Norway

Background/Objectives: Cervical cancer remains a major public health problem in Mexico. Self-sampling for HPV testing increases access to screening and population coverage. E6/E7 mRNA detection has been identified as a potential biomarker for triage of DNA-positive women. The aim of this study was to compare self-sampling versus clinician-sampling for complete molecular HPV diagnostics, with respect to sample quality, positivity rates and relevance for referral to colposcopy

Methods: 505 women aged 30-65 years at Mexico General Hospital underwent self-sampling (Mia by XytoTest) and clinician-sampling (Cervex by Rovers). Samples were tested for HR-HPV DNA (RealTime hrHPV, Abbott (14 types)) and E6/E7 mRNA (PreTect HPV-Proofer`7 (7 hrHPV-types in the 9-valent vaccine)).

Results: HPV-DNA prevalence was 22.8% in self-collected versus 19.2% in clinician-collected samples (P=0.19). Overexpression of mRNA E6/E7 from 7 HPV types was 7.1% and 6.3%, respectively (P=0.71). Overall agreement between the two collection methods was fair, with a concordance rate of 78.2% (390/505), k=0.34 (95% CI: 0.25-0.44), P<0.001, for the HPV-DNA test and 92.5% (467/505), k=0.40 (95% CI: 0.25-0.56), P<0.001, for the mRNA test, respectively. The self-sampled aliquot contained about 3 times more cells compared to clinician taken aliquot; 1.87 million cells/ml versus 0.63 million cells/ml, respectively.

Conclusions: Self-sampling (Mia by XytoTest) is as reliable as clinician-sampling for HPV testing and allows direct HPV mRNA genotyping. Self-sampling is an effective strategy to reach under screened women. The high prevalence of DNA positive results reflects the need for reflex triage, thereby reducing unnecessary colposcopies, women's uncertainties, and cost. A low positivity rate of concurrent DNA+/mRNA+ (6.3%) effectively discriminates women warranted for immediate colposcopy/biopsy from return to follow-up and suggests longer follow-up interval for single DNA+ women. Such a strategy will inevitably reduce over-referral for colposcopy but needs clinical and cost-benefit assessment in prospective studies.

Bottari Fabio
Italy
Bottari Fabio
Italy

#3748

THE EXTENDED VALIDATION OF HUMAN PAPILLOMAVIRUS ASSAYS AND COLLECTION DEVICES FOR HPV TESTING (EXTENDED VALHUDES): THE IEO EXPERIENCE.

13 - Self-sampling

Bottari F[1,2], Iacobone A[2,3], Passerini R[1], Pietri R[4], Piana A[2,5], Guerrieri M[3], Martella S[3], Preti E[3], Cocuzza C[6]

[1]European Institute of Oncology, Division of Laboratory Medicine, Milan, Italy
[2]University of Sassari, Department of Biomedical Sciences, Sassari, Italy
[3]European Institute of Oncology, Unit of Preventive , Milan, Italy
[4]ATS Sardegna, Coordinamento Consultori Familiari, ASSL Sassari, Sassari, Italy
[5]University of Sassari, Department of Medical, Surgical and Experimental Sciences, Sassari, Italy
[6]University of Milano-Bicocca, Department of Medicine and Surgery, Monza, Italy
[7]Belgian Cancer Centre, Sciensano, Unit of Cancer Epidemiology, Brussels, Belgium

Background/Objectives: Previous studies demonstrated that PCR-based HPV tests are similarly accurate on self-produced samples as on clinician-collected cervical samples [1] but validation of HPV assays in combination with the self-sample collection devices for are required [2]. This study, named Extended VALHUDES (Extended VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples), aims to extend a previous VALHUDES validation of BD Onclarity HPV Assay in combination with a new vaginal sample collection device, COPAN FLOQ Swab, on BD Viper LT automated instrument.

Methods: A total of 300 women referred to the European Institute of Oncology (IEO) in Milan and a Coordinamento Consultori Familiari, ASSL Sassari, ATS Sardegna because of a previous cervical abnormality were enrolled after obtaining informed consent. A dry vaginal self-sample was collected by each enrolled woman and transferred to BD HPV LBC Self-Collection diluent (3 mL) tubes on arrival at IEO laboratory and tested with BD Onclarity on the BD Viper LT at IEO. An aliquot of the clinician-collected cervical sample PreservCyt media was transferred to a BD HPV LBC diluent tube. Vaginal swab and the LBC cervical specimen were tested with BD Onclarity on the BD Viper LT at IEO to compare performance.

Results: 296 of the 300 women had evaluable results from both the vaginal self-sample and the clinician collected cervical specimen. 172 of the 296 women had cervical biopsies obtained during the colposcopy, with histopathology reports. There were 79 women with ≥CIN2 histology and 48 women ≥CIN3. The overall agreement between vaginal self-sample and cervical sample for BD Onclarity HPV Assay on BD Viper LT in IEO laboratory was 264/296 (89.2%; CI 79.1-99.3%), Kappa=0.75 (CI 0.630-0.867). The absolute sensitivity for the vaginal self-sample and cervical sample in CIN2+ detection was 89.9% and 88.6% respectively and the absolute specificity was 38.7% and 40.9% respectively.

Conclusions: This data demonstrates a good concordance and sensitivity between HPV detection on vaginal samples vs BD Onclarity HPV Assay (Viper LT) on clinician-collected samples.

References: [1] Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018 Dec 5;363:k4823. [2] Arbyn M, Peeters E, Benoy I, Vanden Broeck D, Bogers J, De Sutter P, Donders G, Tjalma W, Weyers S, Cuschieri K, Poljak M, Bonde J, Cocuzza C, Zhao FH, Van Keer S, Vorsters A. VALHUDES: a protocol for VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples. J Clin Virol. 2018; 117: 52-56

Hesselink Bart
Netherlands

Bart Hesselink
Netherlands

#3576

VALIDATION OF THE CLINICAL PERFORMANCE AND REPRODUCIBILITY OF THE NEUMODX HPV ASSAY SELF-SAMPLE WORKFLOW

13 - Self-sampling

Background/Objectives: HPV testing on self-collected (cervico-)vaginal specimens (HPV self-sampling) has similar clinical accuracy for CIN2/3+ compared to clinician-collected samples when performed with a clinically validated PCR-based assay. Therefore HPV self-sampling is a suitable alternative primary screening method for routine cervical screening. However, validation of the HPV self-sampling workflow (i.e., collection device, sample preparation protocol, and HPV test) remains necessary, because use of an HPV test that is clinically validated for clinician-collected samples may not automatically result in high clinical accuracy when applied to self-collected specimens (Belinson et al, 2012).The NeuMoDxTM HPV Assay targets the E7 region of 15 (probably) high risk HPV (hrHPV) types (HPV16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -67, and -68) and confers partial genotyping by individually reporting HPV16 and HPV18, and concurrently detects the 13 other common high-risk types as a pool. The NeuMoDxTM HPV Assay has been clinically validated for use in cervical screening on clinician-collected cervical samples collected in both PreservCyt and SurePath collection medium using the international guidelines for HPV DNA test requirements for primary cervical screening. Recently, the NeuMoDxTM HPV Assay self-sample workflow has been developed. Performance data of the NeuMoDx HPV Assay self-sample workflow will be presented.

Methods:

Results:

Conclusions:

Smith Jennifer
United States

Lee Fan

#3933

SELF-COLLECTION TEST PERFORMANCE FOR HIGH-RISK HPV RNA DETECTION AMONG HIV-POSITIVE AND HIV-NEGATIVE WOMEN ENGAGED IN FEMALE SEX WORK IN KENYA

34 - Sexually transmitted diseases and HIV infection

Lee F[1], Islam J[2], Mutua M[3,4], Kabare E[3,4], Manguro G[5,6], Waweru W[3,4], Mandaliya K[7], Shafi J[3,4], Mcclelland S[3,4], Smith J[10,11]

[1]Lineberger Cancer Center, University of North Carolina, Chapel hill, United states
[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel hill, United states
[3]Department of Global Health, University of Washington, Seattle, United states
[4]Department of Epidemiology, University of Washington, Seattle, United states
[5]Pathcare Laboratories, Mombasa, Kenya
[6]Gent University, Faculty of Medicine and Health Sciences, Gent, Belgium
[7]International Centre for Reproductive Health, , Kenya
[8]Department of Medicine, University of Washington, Seattle, United states
[9]Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya
[10]Cancer Epidemiology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, United states
[11]Department of Obstetrics and Gynecology, University of North Carolina, Chapel hill, United states

Background/Objectives: In low and middle-income countries, WHO recommends primary HPV testing for cervical cancer screening where available. Self-collection is also recommended given its potential to overcome screening barriers. We examine self-collected high-risk HPV RNA testing for the detection of histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2/3) among women engaged in female sex work (FSW) in Mombasa, Kenya. We report hrHPV prevalence among HIV-positive and HIV-negative women, and determine predictors of baseline hrHPV infection and CIN2/3 outcomes.

Methods: 400 Kenyan women (193 HIV-positive, 206 HIV-negative) who were ≥18 years old, non-pregnant and without a history of treatment for cervical precancer participated (2013-2018). Baseline demographics were obtained at study enrollment. Screening procedures included self-collection of cervico-vaginal via a Viba cytobrush (Rovers) and provider-collection of cervical samples, inspection with acetic acid (VIA) and Pap smear screening. APTIMA HPV Assay (Hologic Corporation) was used to detect E6/E7 oncogene mRNA of 14 hrHPV types. Abnormal results from any screening method and 10% random sample of participants with negative results on all tests underwent colposcopy exam. Cervical biopsies were obtained from lesions, and if no lesions were identified, taken at 12 and 6 o'clock at the squamo-columnar junction. Sensitivity and specificity analyses were used to evaluate test performance for CIN2+ detection. Risk factors for hrHPV positivity and CIN2,3 disease were determined via multi-variable logistic regression.

Results: 400 Kenyan women (193 HIV-positive, 206 HIV-negative) who were ≥18 years old, non-pregnant and without a history of treatment for cervical precancer participated (2013-2018). Baseline demographics were obtained at study enrollment. Screening procedures included self-collection of cervico-vaginal via a Viba cytobrush (Rovers) and provider-collection of cervical samples, inspection with acetic acid (VIA) and Pap smear screening. APTIMA HPV Assay (Hologic Corporation) was used to detect E6/E7 oncogene mRNA of 14 hrHPV types. Abnormal results from any screening method and 10% random sample of participants with negative results on all tests underwent colposcopy exam. Cervical biopsies were obtained from lesions, and if no lesions were identified, taken at 12 and 6 o'clock at the squamo-columnar junction. Sensitivity and specificity analyses were used to evaluate test performance for CIN2+ detection. Risk factors for hrHPV positivity and CIN2,3 disease were determined via multi-variable logistic regression.

Conclusions: Self-collection for hrHPV testing performed similarly to provider-collection in this high-risk cohort. The relatively higher sensitivity of mRNA-based hrHPV testing compared to cytology for the detection of clinically relevant cervical disease is important in this high-risk cohort.

FC15 - Self-sampling 2

Sonne Si Brask
Denmark
Sonne Si Brask
Denmark

#3745

A RANDOMIZED, LARGE SCALE COMPARISON OF DIRECT MAIL VERSUS OPT-IN HPV SELF-SAMPLING INVITATION STRATEGY: PARTICIPATION RATES, PARTICIPANTS, FOLLOW-UP AND COST OF LAST ATTENDER

13 - Self-sampling

Sonne S[1], Pedersen B[1], Andreasen E[1], Ejegod D[1], Pedersen H[1], Bonde J[1]

[1]Molecular Pathology, Dept. Pathology, AHH-Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark

Background/Objectives: Background HPV self-sampling is increasingly being offered as an alternative to ordinary screening. However, which invitation strategy yields the best cost-benefit in terms of participation versus number of self-sampling kits distributed. Is it directly mailing kits to all eligible women or an Opt-in strategy where kits are mailed only to those who actively accept the offer? In a large scale, randomized, study we evaluated participation and number of HPV self-sampling kits distributed by a Direct mail and Opt-in approach.

Methods: Methods Women with no registered cervical screening sample in at least 4 years were randomly assigned to either the Direct mail group (N=9,634, period June-Sept 2020) or the Opt-in group (N=39,754, period Sept 2020-January 2021). In the Direct mail group, all women received the HPV self-sample kit whereas the Opt-in group received the HPV self-sampling invitation by national e-mail with instructions for registration. Reminder letters to return the HPV self-sampling kit for analysis were sent 60 days after shipping the kit. For the Opt-in arm, only women who registered for a test kit received a reminder. Follow-up information was registered and retrieved from the Danish National Pathology Database (Patobank), latest data retrieval November 2021. The test kit contained an Evalyn self-sampling brush. Upon arrival in the lab, the sample was analyzed on a VIPER LT, using the Onclarity HPV assay from BD. Women found HPV positive by self-sampling were referred for follow up with a clinician collected liquid based cytology sample within 3 months.

Results: Results In the Direct-Mail arm, 25% (N=2,406) returned the self-sampling kit and in the Opt-in arm, 20% (7,994) returned the kit. In the Direct mail arm, 7,850 women received a reminder with 9% (N=685) responding. In the Opt-in arm, 7,462 received a reminder resulting in 30% (N=2,222) samples returned. The overall HR-HPV prevalence was 14.6%, and 89% of the HPV positive women adhered to the follow up recommendation, with no difference between the two arms, respectively. For each woman included in the Direct mail group, 3 tests were never returned, whereas 0.7 tests were lost for each participant from the Opt-in group. More women participated by direct mail, but at a cost of >13 HPV self-sample kits per additional woman compared to the Opt-in approach.

Conclusions: Conclusions Both invitation approaches returned a high number of participating women. A reminder strategy yielded a significant number of additional participants in both groups, and women in general adhered to the follow up recommendation. Finally, the cost of conducting a Direct mail approach seems rather high when balanced against the yield in participants.

Kaljouw Sylvia
Netherlands

Kaljouw Sylvia
Netherlands

#3707

REALISTIC POPULATION-BASED COST-EFFECTIVENESS ESTIMATES FOR WIDER DEPLOYMENT OF HRHPV SELF-SAMPLING: A MODELLING STUDY

13 - Self-sampling

Kaljouw S[1], Jansen E[1], De Kok I[1]

[1]Erasmus Medical Center, Rotterdam, Netherlands

Background/Objectives: Background/Objectives: The hrHPV self-test has been suggested as an alternative to the hrHPV-test administered by the general practitioner to reach women who might otherwise not participate in cervical cancer screening. Recently, population-based data on loss-to-follow-up (LTFU) for reflex cytology (after self-sampling) (-7.8% LTFU) and relative sensitivity of the self-test have been reported in the Netherlands (0.94 relative sensitivity for CIN3+). We aimed to present population-based realistic cost-effectiveness estimates of wider deployment of self-sampling, taking into account this recent data.

Methods: Methods: We used simulation model MISCAN-Cervix to calculate the cost-effectiveness of several self-test deployment strategies based on feasible options to adjust the guideline (such as actively sending the self-test to all women, to 30-year old women or with the reminder letter) (Table 1). Scenarios varied in the percentage of originally participating women using self-sampling and the percentage of original non-attenders using self-sampling. Main outcome measures were life years gained, QALYs gained and costs compared to a scenario without screening. Table 1: Overview of strategies included in the analysis. The strategies vary in the percentage of self-sampling of all used tests without extra attendance and the percentage of extra attendance using self-sampling. Extra attendance (using self-sampling) Self-test deployment strategy % self-sampling of all used primary tests (without extra attendance) No extra attendance 10% of non-attenders 30% of non-attenders Women need to actively request the self-test 7% self-sampling all ages Current Send self-test with the reminder letter 7% self-sampling all ages (A) A10 A30 Send self-test to 30-year old women 50% self-sampling at 30 years old (B) B0 B10 B30 Send self-test to all women 30% self-sampling all ages (C) C0 C10 C30 Send self-test to all women 40% self-sampling all ages (D) D0 D10 D30 Send self-test to all women 50% self-sampling all ages (E) E0 E10 E30 * If two self-sampling percentages are given for a certain age, the highest percentage will be used when strategies are combined.

Results: Preliminary results: There was very little relative variation in the life years gained and QALYs gained for any of the scenarios (0.00-0.01%), however in absolute values 134 life years per 100,000 women can be saved if the attendance increases by 30% of non-attenders. Replacing 40% of the hrHPV tests at the GP by self-sampling without additional attendance leads to a decrease in costs (-3%), whereas increasing the attendance with the same strategy leads to an increase of 8% in costs. The highest costs are obtained when 7% of women use self-sampling with 30% additional attendance (+13%).

Conclusions: Conclusions: Taking into account the slightly lower relative sensitivity of self-sampling and loss-to-follow-up after self-sampling, we found that wider deployment of self-sampling is desirable. High attendance in combination with a high percentage of self-sampling is most cost-effective, due to the relatively low cost and slightly lower relative sensitivity of self-sampling compared to GP-based hrHPV-testing. More analyses are currently being done.

Biederman Erika
United States

Biederman Erika

#3742

FACTORS ASSOCIATED WITH MAILED RETURN OF SELF-COLLECTION FOR HUMAN PAPILLOMAVIRUS (HPV) TESTING

13 - Self-sampling

Zimet G[2], Champion V[3]

[1]The James Ohio State University Comprehensive Cancer Center, Columbus, ohio, United states
[2]Indiana University School of Medicine, Indianapolis, indiana, United states
[3]Indiana University School of Nursing, Indianapolis, in, United states

Background/Objectives: Low-income women in the United States (U.S.) have greater odds of dying from cervical cancer and lower cervical cancer screening rates compared to higher income women. Self-collection for human papillomavirus (HPV) testing has demonstrated acceptability in previous studies, but up to 50% of low-income women do not return self-collection kits, and characteristics of those who complete and return a self-collection kit have not been investigated. The purpose of the current study was to examine how sociodemographic factors (age, education, income, insurance and marital status, and race), health-related variables (seeing a provider in the past year, body mass index, smoking status, history of abnormal Papanicolaou test), and relative advantages were associated with mailed return of self-collection kits (returners vs. non-returners).

Methods: Low-income women (n=168) aged 30-65 with no history of hysterectomy who were not up to date with U.S. Preventive Services Task Force cervical cancer screening guidelines (i.e., no Papanicolaou [Pap] test in the past 3 years, HPV test in the past 5 years, or Pap and HPV test in the past 5 years) were recruited from Midwestern food pantries and online (Craigslist and Facebook). Women completed a survey and were mailed self-collection kits that could be mailed back. Bivariate analyses were initially conducted, with significant bivariate predictors subsequently entered in a multivariable logistic regression analysis to evaluate predictors of mailed return of self-collection kits.

Results: In bivariate analyses, age, education, body mass index, and relative advantages were significantly different between returners and non-returners and thus entered the multivariable logistic regression. Women in the 40-49 age-group vs. the 30-39 age-group (Odds ratio [OR]=3.32, 95% Confidence Interval [95%CI]=1.44,7.69), college education or more vs. high school education or less (OR=6.47, 95%CI=1.61,25.96), obese vs. non-obese (OR=2.24, 95%CI=1.06,4.72), and with a higher relative advantages score (OR=1.09, 95%CI=1.01,1.20), had greater odds of returning a kit.

Conclusions: Interventionists could use results from the current study to target women who are not in the 40-49 age group, college educated, obese, or who have a higher relative advantages score with an intervention to increase self-collection. Future studies should examine these results in a larger, more diverse sample.

Pedersen Birgitte
Denmark

Pedersen Birgitte Tonnes
Denmark

#3322

HPV SELF-SAMPLING IN THE CAPITAL REGION OF DENMARK - NEW OPERATIONAL EXPERIENCES

13 - Self-sampling

Pedersen B[1], Pedersen H[1], Serizawa R[1], Ejegod D[1], Bonde J[1]

[1]Department of Pathology, Copenhagen University Hospital AHH-Hvidovre, Hvidovre, Denmark

Background/Objectives: The Danish cervical cancer screening program is a free-of-charge cancer prevention program for all Danish resident women between 23 and 65 years. The coverage is 73%, but screening attendance is slowly declining. Notwithstanding, almost half of all newly diagnosed cervical cancers are found among screening non-attenders. To increase screening attendance, the Capital Region of Denmark implemented HPV self-sampling as an alternative offer to women not attending the regular screening offer. Operational experiences from the set-up of the self-sampling offer are presented here.

Methods: This was an opt-in offer to 57,717 screening non-attending women in 2017-2018. The women received an invitation letter and could opt-in by letter, phone, e-mail or webpage. Invitation and return-of-kit reminders were used in the set-up. HPV positive women were recommended to go to their General Practitioner (GP) for a follow-up sample. HPV negative women returned to the ordinary screening program.

Results: Of all invited women, 27% opted in. The purpose designed web-platform was the most frequent used method of response, 63% opted in by the HPV-self sampling webpage. A significant association between age and response methods was found ($p<0.0001$). Women aged 27-29 years and 30-39 years used the webpage more often compared to women above the age of 40 years, whereas women above the age of 50 years more often used letter for registration compared to the other age groups. Use of invitation and return-of-kit reminders generated 8.6% and 6.1% additional responses and participation, respectively. Overall, 17% returned the HPV self-sampling kit for analysis. In addition, 14% had a regular clinician collected screening sample after receiving the invitation for self-sampling, leading to a total screening of 31% women after invitation. HPV prevalence was 15%, amongst those, 92% adhered to the recommended follow-up.

Conclusions: The frequent use of the HPV self-sample website when responding to the invitation and the diversity in response method dependent on the age of the invited woman emphasizes the benefit of not only novel technology, but also a flexibility in response methods to meet different preferences in the screening population. The additional participation generated by an active reminder strategy underlines the importance of timely communication in screening programs. The findings from this study are useful in the future optimization of cervical cancer screening by HPV self-sampling.

Jentschke Matthias
Germany

Jentschke Matthias
Germany

#3608

HaSCo Study: First results of a pilot study for systematic HPV self-sampling for non-responders to the cervical cancer screening program

13 - Self-sampling

Jentschke M[1], Gross S[1], Steinkasserer L[1], Neuhaus B[2], Geyer S[3], Koch A[4], Hillemanns P[1]

[1]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

[2]Center for clinical studies (ZKS), Hannover Medical School, Hannover, Germany

[3]Medical Sociology Unit, Hannover Medical School, Hannover, Germany

[4]Institute of Biometry, Hannover Medical School, Hannover, Germany

Background/Objectives: In this pilot study we evaluate a systematic approach towards human papillomavirus (HPV) self-sampling for non-responders to the German cervical cancer screening program. In 2020, the renewed organized screening program with co-testing (HPV test + cytology) in 3-yearly intervals was started for all women 35 years and older. In the past, the participation rate was around 70% in a time frame of three years. The non-participators are at higher risk to develop invasive cervical cancer. The willingness to participate can be improved by offering self-sampling devices for home-based use. Based on this information, the Hannover Self-Collection study was started to examine the response rate and practicability of a systematic self-sampling approach.

Methods: 20.000 women aged 30 to 65 years living in the city and region of Hannover, Lower Saxony were randomly included. 10.000 women directly received a self-sampling kit, the other 10.000 a letter of information and option to participate in the study (opt-out vs. opt-in strategy). Stratifications were be made by age (7 cohorts) and area of living (city vs rural). Women tested positive for high-risk HPV (PCR-based HPV assay) were prompted to get a cytological smear by their gynecologist. Women with normal cytology will be re-checked after 6 months. Suspicious cytology results lead to an immediate colposcopy.

Results: The first stage of the study is executed between January and March 2022. First results will be presented at the congress.

Conclusions: To get hold of non-responders to cervical cancer screening programs, self-sampling for HPV is a promising option. Aim of this study is to generate an overall recommendation to improve cervical cancer screening in Germany, especially for non-responders.
This study is supported by Deutsche Krebshilfe.

Payrich Eva-maria
Germany

Payrich Eva-maria
Germany

#3620

THE EMERGING ROLE AND OPINION ABOUT IMPLEMENTATION OF HPV SELF-SAMPLING IN GERMANY: A MIXED METHODS STUDY

13 - Self-sampling

Payrich E[1], Skof A[1], Struck M[1], Thies S[1], Schreckenberger C[1], Kaufmann A[1]

[1]Klinik für Gynäkologie, Charité Universitätsmedizin Berlin – Berlin (Germany) corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Gynaecology, Berlin, Germany

Background/Objectives: The risk of developing cervical cancer is increased for non-participants in screening programs. In 2019, only 47.7% of all women entitled participated in the opportunistic screening program in Germany. Self-sampling increases participation rates (1) and is as sensitive as HPV tests performed on clinician samples (2). There are few qualitative data on opinions by women and physicians. Our aim was to involve potential users and learn about experiences, expectations, and possible applications of Self-sampling

Methods: This mixed-methods-study was a substudy of the FACTS project, a study to validate whether the use of the QuantiGene-Molecular-Profiling-Histology assay (QG-MPH) can triage women screened positive by cytology or HPV-tests. All included women (n=696) were asked to perform Self-sampling with the Evalyn® Brush in addition to a gynaecological specimen and to fill a questionnaire. Additionally, 25 one-to-one semi-structured interviews with FACTS participants (n=9), women recruited by a social media call (n=5), study gynaecologists (n=5) and gynaecologists not involved in the study (n=6) were performed.

Results: The Self-sampling participation rate was 86.6%. According to 496 questionnaires evaluated 413 (83.3%) women median age 40 (20-77) had participated in the screening several times. The application of Self-sampling and the Self-sampling compared to a gynaecological smear was described as "good or very good" by 89.3% and 82.9%, respectively. Nevertheless, all interviewed women (n=14) stated that they would not prefer Self-sampling to a visit to the gynaecologist, which was a concern by most of the gynaecologists interviewed. Self-sampling was seen more as a way of reassuring oneself, not having to extend screening intervals due to time constraints and an opportunity of female empowerment in gynaecological aspects. However, women and gynaecologists interviewed also indicated concerns about mishandling of the Self-sampling brush, lack of control opportunities and further physician involvement when results are abnormal.

Conclusions: Self-sampling as an additional option to office-based screening is well accepted among German women. However, the Self-sampling option is stated not to replace a visit to the gynaecologist, although this is concerned by many physicians. It would be conceivable to implement Self-sampling in addition to the office-based screening to facilitate access and to meet the desire for self-determination. It must be considered that our study mainly included women from urban areas with a high gynaecological office density and high screening participation.

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Korsgaard Andreasen Emilie
Denmark

Korsgaard Andreasen Emilie
Denmark

#3616

ANALYTICAL STABILITY OF ROVERS EVALYN AND COPAN FLOQSWAB HPV SELF-SAMPLING DEVICES; IMPLICATIONS FOR USE

13 - Self-sampling

[1]Molecular Pathology, Dept. Pathology, AHH-Hvidovre Hospital, Copenhagen University Hospital, Copenhagen, Denmark

Background/Objectives: HPV self-sampling is emerging as an alternative sampling modality to facilitate increased participation in cervical cancer screening. Typically, self-sampling kits are mailed to women who subsequently return them for analysis. In this process, the self-sample will be transported under diverse temperature conditions and time-to-analysis depends on the postal infrastructure. Here, we assess the analytical stability of the Rovers Evalyn and COPAN FLOQSwab self-sampling brushes under low, normal, and extreme temperatures and during prolonged storage after sampling.

Methods: The analytical quality was assessed using the human beta-globin (HBB) and HPV16 Ct scores of the BD Onclarity HPV test. Two endpoints were used: rate of analytically invalid self-sampling brushes upon testing and changes in Ct scores. The assay cut-off for HBB is Ct 34.2, the cut-off for HPV16 is Ct 38.3 (manufacturers specifications). A pool of 120mL non-fixated, confirmed HPV16 positive cervical samples constituted a master sample. The FLOQSwab brushes were kept at three different temperatures (4°C, room temperature, RT, and 40°C) and four different timepoints (0 days, 4 weeks, 8 weeks, and 16 weeks). The Evalyn brushes were kept at RT for the first timepoint (0 days) and 40°C for the remaining timepoints (4 weeks, 8 weeks, 16 weeks). A total of 300 FLOQSwab and 120 Evalyn brushes were prepared, with 30 brushes per time and temperature point. A similar set of data on 50°C is in preparation and will be reported too. The study is conducted as a quality development study approved by AHH-Hvidovre Hospital.

Results: The proportion of analytical invalid samples increased with time and temperature. For FLOQSwab, the proportion of invalids measured by HBB at RT were 20% at 4 weeks and 70% at 16 weeks. At 40°C, the number of invalid samples was 73.3% at 4 weeks and 100% at both 8 and 16 weeks. For the Evalyn brush, the proportion of invalid samples was 3.3% at RT and 60% at 40°C for timepoints 4 and 16 weeks. Time and temperature affected the analytical quality of samples. At RT, FLOQSwap showed a T0 mean HPV16 Ct of 27.43 (N=30). At RT, T16 weeks, the overall mean HPV16 Ct was 32.12 (N=30) and at 40°C, T16 weeks, the mean Ct-value was 38.13 (N=12). For the Evalyn self-sampling device at RT, the reference value at T0 was a mean HPV16 Ct of 28.93. At T16, 40°C the mean HPV16 Ct was 27.90 (N=29).

Conclusions: Overall, the FLOQSwab was less analytical stable than the Evalyn brush. The implications of these study data are that Evalyn can be safely used with prolonged transport at RT, whereas FLOQSwab has a time limited stability at no longer than 4 weeks. Increased ambient temperature to 40°C affected both brush types negatively, with FLOQSwab being less analytically stable than Evalyn.

Smith Jennifer
United States

Pretsch Peyton
United States

#3931

EFFECT OF HPV SELF-COLLECTION ON CERVICAL CANCER SCREENING COMPLETION AMONG LOW-INCOME, UNDER-SCREENED PEOPLE WITH A CERVIX IN THE US: MY BODY, MY TEST 3 STUDY

11 - Screening for women difficult to reach

Pretsch P[1], Spees L[2,3], Rohner E[1], Wheeler S[1,2], Hudgens M[4], Sanusi B[5], Des Marais A[1], Jackson S[1], Barclay L[6], Carter A[7], Brewer N[3,8], Smith J[1,3]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel hill, United states

[2]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel hill, United states

[3]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel hill, United states

[4]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel hill, United states

[5]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, United states

[6]American Sexual Health Association, Research triangle park, United states

[7]Laboratory Corporation of America Holdings, Burlington, United states

[8]Department of Health Behavior, Gillings School of Global Public Health, Chapel hill, United states

Background/Objectives: Most cervical cancer cases in the US occur among under-screened people with a cervix. Mailed, at-home HPV self-collection has the potential to reduce barriers and increase screening coverage among under-screened people with a cervix. We conducted a randomized controlled trial to assess the effectiveness of mailing HPV self-collection kits to increase completion of cervical cancer screening among low-income, under-screened people with a cervix.

Methods: My Body My Test-3 study participants came from 22 counties in North Carolina, US. Eligibility included being aged 25-64 years, uninsured or enrolled in Medicaid or Medicare, reporting an income of ≤250% of US Federal Poverty Level, and overdue for screening per national guidelines (Pap >4 years or high-risk HPV test >6 years ago). Participants randomized to the intervention arm received an HPV self-collection kit and received scheduling assistance to obtain a free screening appointment. In the control arm, participants received scheduling assistance alone. Self-collection kits included illustrated instructions and a Viba self-collection brush (Rovers). Cervico-vaginal samples were tested for high-risk HPV RNA (Aptima, Hologic). The primary trial outcome was completion of screening within 6 months of study enrollment: defined as testing HPV-negative on self-collected samples (intervention arm) or attending in-clinic screening. Our primary analysis applied an intention-to-treat (ITT) principle to compare screening completion between study arms.

Results: We randomized 665 participants to intervention and control arms in a 2:1 ratio. Median age was 42 (range 25-61) years and median time since last screening was 5 (range 4-25) years. Screening completion was higher in the intervention arm than in the control arm (72% vs. 37%; relative risk [RR]=1.93, 95% confidence interval [CI]: 1.62-2.32) in primary ITT analyses. Among 329 intervention participants who returned a kit with valid test results, 16% were HPV positive. Among all 665 participants, 3.5% had abnormal cytology (4.1% in intervention arm, 2.2% in control), and 1.4% were referred for colposcopy (1.6% in intervention, 0.9% in control). Screening detected CIN2+ in 0.5% of the intervention and none of the control participants.

Conclusions: Mailed HPV self-collection kits with scheduling assistance led to more cervical cancer screening completion among low-income, under-screened people with a cervix as compared to scheduling assistance alone. At-home HPV self-collection testing has the potential to increase screening completion among infrequently screened people with a cervix in the US.

Smith Jennifer
United States

Fan Lee

#3917

Prevalence of high-risk HPV by RNA assay in home self-collected samples among underscreened people in North Carolina

11 - Screening for women difficult to reach

Fan L[1], Bukowski A[2], P. Spees L[3,4], B. Wheeler S[3,4], T. Brewer N[4,5], Sanusi B[6], G. Hudgens M[7], Jackson S[2], Barclay L[8], Carter A[9], H. Tang J[1], S. Smith J[2,5]

[1]Laboratory Corporation of America Holdings, Burlington, United states

[2]American Sexual Health Association, Research triangle park, United states

[3]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel hill, United states

[4]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, United states

[5]Department of Health Behavior, Gillings School of Public Health, University of North Carolina, Chapel hill, United states

[6]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel hill, United states

[7]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina, Chapel hill, United states

[8]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel hill, United states

[9]Department of Obstetrics and Gynecology, University of North Carolina, Chapel hill, United states

Background/Objectives: Low-income and uninsured people with a cervix (PWC) are at highest risk of being underscreened for cervical cancer. We evaluated the prevalence of high-risk HPV (hrHPV) on home self-collected samples, as well as rates of in-clinic follow-up and risk factors associated with hrHPV positivity in this at-risk population

Methods: My-Body-My-Test-3 was conducted between 2016-2019 in North Carolina among individuals aged 25-64 years, overdue for cervical cancer screening, and with incomes of <250% of the U.S. Federal Poverty Level. Our analytic sample included participants randomized to the self-collection arm who returned self-collected cervico-vaginal brush samples for HPV testing (n=329). Samples were tested for 14 hrHPV types by an HPV RNA assay and further genotyped for HPV 16 and HPV 18/45. We examined behavioral risk factors for hrHPV positivity using logistic regression and between-subjects t-tests.

Results: HrHPV RNA prevalence was 16% (n=52/329) in self-collected samples. Of the hrHPVpositive participants, 24 (46%) presented for in-clinic cervical cancer screening, compared to 56 (20%) of hrHPV-negative participants. Those with ≥2 sexual partners in the past year were twice as likely to be hrHPV positive in adjusted analyses (adjusted OR=2.00 (95% CI: 1.03-3.88). HrHPV-positive and negative participants had similar attitudes towards screening, with the exception of hrHPV-positive participants who reported a lower perceived risk of cervical cancer than those who were hrHPV-negative (p<.05).

Conclusions: The hrHPV RNA prevalence was similar to findings in other underscreened PWC in the US. Efforts to reach underscreened PWC is critical for cervical cancer prevention. Future studies aimed at home self-collection should address methods of increasing clinic attendance and completion of treatment among those with HPV-positive results.

HN05- HPV and H&N Forum - Carcinogenesis & molecular characterization

Klein Sebastien
Germany

Klein Sebastian
Germany

#3986

Deep learning in histological samples of HPV associated oropharyngeal tumors

30 - HPV and oropharynx / Head and neck cancer

Klein S[1,2], Klussmann J[3]

[1]Department of Hematology and Stem Cell Transplantation, Essen, Germany

[2]Institute for Pathology, University Hospital Cologne, Cologne, Germany

[3]Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty, University Hospital Cologne, Cologne, Germany

Background/Objectives:
Human papillomavirus (HPV) in oropharyngeal squamous cell carcinoma (OPSCC) is tumorigenic and has been associated with a favorable pr
and in particular deep
learning, has evolved as a powerful tool to predict molecular- and cellular alterations of medical images of various sources.

Methods:
We generated a deep learning-based HPV prediction score (HPV-ps) on regular H&E stains and assessed its performance to predict HPV-asso

Results: Although pathologists were able to diagnose HPV-association from H&E stained slides, (AUC=0.74, median of four observers) the inter-rater reliability was minimal (Light's Kappa=0.37; p=0.129), as compared to AUC=0.8 using the HPV-ps within two independent cohorts (n=273). The HPV-ps identified individuals with a favorable prognosis in a total of 594 patients from three cohorts (Giessen, OPSCC, HR=0.55, p<0.0001; Cologne, OPSCC, HR=0.44, p=0.0027; TCGA, non-OPSCC Head and Neck, HR=0.69, p=0.0073). Interestingly, the HPV-ps further stratified patients when combined with p16-status (Giessen, HR=0.06, p<0.0001; Cologne, HR=0.3, p=0.046).

Conclusions: Detection of HPV-association in OPSCC using deep learning with help of regular H&E stains may either be used as a single biomarker-or in combination with p16-status-to identify OPSCC patients with a favorable prognosis potentially outperforming combined HPV-DNA/p16-status as a biomarker for patient stratification. We anticipate that prediction of HPV association by deep learning from histology of routine histological samples of OPSCC tumors may be a viable biomarker in the near future.

References: Sebastian Klein, Alexander Quaas, Jennifer Quantius, Heike Löser, Jörn Meinel, Martin Peifer, Steffen Wagner, Stefan Gattenlöhner, Claus Wittekindt, Magnus von Knebel Doeberitz, Elena-Sophie Prigge, Christine Langer, Ka-Won Noh, Margaret Maltseva, Hans Christian Reinhardt, Reinhard Büttner, Jens Peter Klussmann, Nora Wuerdemann; Deep Learning Predicts HPV Association in Oropharyngeal Squamous Cell Carcinomas and Identifies Patients with a Favorable Prognosis Using Regular H&E Stains. Clin Cancer Res 15 February 2021; 27 (4): 1131-1138. https://doi.org/10.1158/1078-0432.CCR-20-3596

Puram Sidharth
United States

Puram Sidharth
United States

#3949

Cellular states are coupled to genomic and viral heterogeneity in HPV-related oropharyngeal carcinoma

30 - HPV and oropharynx / Head and neck cancer

Puram S[1]

[1]Washington University, St. louis, United states

Background/Objectives: Define the heterogeneous cell states present in HPV-related oropharyngeal cancer and determine their impact on disease pathogenesis.

Methods: Single cell RNA-sequencing of HPV-related and HPV-negative oropharyngeal tumors in a prospectively collected cohort (n=15).

Results: We uncovered a high level of cellular diversity within and between tumors. First, we detect diverse chromosomal aberrations within individual tumors, suggesting remarkable genomic instability and enabling the identification of malignant cells even at pathologically-negative margins. Second, we uncover diversity with respect to HNSCC subtypes and other cellular states such as the cell cycle, senescence, and epithelial-mesenchymal transitions. Third, we find diversity in the expression of viral genes within HPV-positive tumors. These findings suggest that expression diversity in HPV oropharyngeal tumor must be taken into account during diagnosis and treatment of HPV-positive tumors, with important ramifications for uncovering patients at risk for poor outcomes among an otherwise largely favorable prognosis.

Conclusions: In summary, our comprehensive single cell analysis of oropharyngeal tumors reveals unappreciated diversity both in host and in viral genes, with critical implications for our understanding of virally-mediated tumors.

Faden Daniel
United States

Faden Daniel
United States

#3987

Circulating Tumor HPV DNA in the Diagnostic and Surgical Settings

30 - HPV and oropharynx / Head and neck cancer

Faden D[1]

[1]Harvard Medical School, Boston, United states
[2]Mass eye and ear, Boston, United states

Background/Objectives: HPV-associated head and neck squamous cell carcinoma (HPV+HNSCC) is the most common HPV-associated malignancy in the United States and continues to increase in incidence. New ultrasensitive methods for detecting, diagnosing, and monitoring HPV+HNSCC are needed. Here, we will review emerging data regarding the use of circulating tumor HPV DNA as both a tool at the time of diagnosis and following surgery.

Methods: We conducted a prospective observational study in 140 subjects (70 cases and 70 controls) to determine if: 1. a noninvasive diagnostic approach for HPV+HNSCC would have improved diagnostic accuracy, lower cost, and shorter diagnostic interval compared with standard approaches, and 2. the clearance kinetics of ctHPVDNA are associated with postoperative disease status. Blood was collected, processed for circulating tumor HPV DNA (ctHPVDNA), and analyzed with custom ddPCR assays for HPV genotypes 16, 18, 33, 35, and 45. Diagnostic performance, cost, and diagnostic interval were calculated for standard clinical workup and compared with a noninvasive approach using ctHPVDNA combined with cross-sectional imaging and physical examination findings. In 33 patients with HPV+OPSCC undergoing surgery, blood was collected before surgery, postoperative days 1 (POD 1), 7, and 30 and with follow-up. A subcohort of 12 patients underwent frequent blood collections in the first 24 hours after surgery to define early clearance kinetics.

Results: Sensitivity and specificity of ctHPVDNA for detecting HPV+HNSCC were 98.4% and 98.6%, respectively. Sensitivity and specificity of a composite noninvasive diagnostic using ctHPVDNA and imaging/physical examination were 95.1% and 98.6%, respectively. Diagnostic accuracy of this noninvasive approach was significantly higher than standard of care (Youden index 0.937 vs. 0.707, P = 0.0006). Costs of noninvasive diagnostic were 36% to 38% less than standard clinical workup and the median diagnostic interval was 26 days less. Following surgery, in patients without pathologic risk factors for recurrence who were observed after surgery, ctHPVDNA rapidly decreased to <1 copy/mL by POD 1 (n = 8/8). In patients with risk factors for macroscopic residual disease, ctHPVDNA was markedly elevated on POD 1 (>350 copies/mL) and remained elevated until adjuvant treatment (n = 3/3). Patients with intermediate POD 1 ctHPVDNA levels (1.2-58.4 copies/mL) all possessed pathologic risk factors for microscopic residual disease (n = 9/9). POD 1 ctHPVDNA levels were higher in patients with known adverse pathologic risk factors such as extranodal extension >1 mm (P = .0481) and with increasing lymph nodes involved (P = .0453) and were further associated with adjuvant treatment received (P = .0076). One of 33 patients had a recurrence that was detected by ctHPVDNA 2 months earlier than clinical detection.

Conclusions: A noninvasive diagnostic approach for HPV+HNSCC demonstrated improved accuracy, reduced cost, and a shorter time to diagnosis compared with standard clinical workup and could be a viable alternative in the future. POD 1 ctHPVDNA levels are associated with the risk of residual disease in patients with HPV+OPSCC undergoing curative intent surgery and thus could be used as a personalized biomarker for selecting adjuvant treatment in the future.

Lewis James
United States

Lewis James
United States

#3992

Pathology-Based HPV Testing in Head and Neck Carcinomas - The Big Questions

09 - HPV testing

Lewis J[1]

[1]Vanderbilt University Medical Center, Nashville, tn, United states

Background/Objectives: Human papillomavirus status (HPV) has become critical for oropharyngeal squamous cell carcinoma (SCC) patients. As the field is evolving, the type of HPV testing, whether with p16 immunohistochemistry alone, HPV-specific testing alone, or a combination of tests, is in flux. Further, cytology aspirate specimens present unique challenges for HPV testing and circulating high risk HPV DNA testing is emerging which may supplant tissue and fine needle aspirate specimen testing completely. Many very big questions with pathology-based HPV testing remain that will be explored in this talk.

Methods: Based on years of experience and as a co-chair of the College of American Pathologists' expert panel of HPV testing in head and neck carcinomas, the presenter will address critical questions in daily practice for oropharyngeal SCC patients.

Results: The four major questions revolve around the "messy middle", or the 5-10% of patients with mismatch of p16 and HPV-specific testing results, around the optimal testing for cytopathology fine needle aspirate specimens from cervical nodal metastases, around how pathology-based testing will evolve if circulating HPV DNA blood testing continues to improve and be used, and around whether (and where) testing of non-oropharyngeal SCCs will finally arrive in practice.

Conclusions: The field is moving rapidly and HPV testing has to evolve to match clinical needs and to apply the best testing for patient risk stratification and prognostication. Availability of more sophisticated and accurate HPV and surrogate marker testing will help to better tailor prognostication and individual patient treatment in oropharyngeal SCC.

FC16 - Immunology and immunotherapy

Suominen Helmi
Finland
Suominen Helmi
Finland

#3567

CHARACTERIZATION OF PERIPHERAL BLOOD T-LYMPHOCYTE SUBSETS AMONG MOTHERS WITH PERSISTENT GENITAL OR ORAL HPV16 INFECTION AND THEIR CHILDREN

05 - Immunology

Suominen H[1], Paaso A[2], Koskimaa H[2], Grenman S[3], Syrjänen K[4], Syrjänen S[2,5], Louvanto K[1,6]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[2]Department of Oral Pathology and Oral Radiology, Institute of Dentistry, Faculty of Medicine, University of Turku, Turku, Finland
[3]Department of Obstetrics and Gynecology, Turku University Hospital and University of Turku, Turku, Finland
[4]Department of Clinical Research, Biohit Oyj, Helsinki, Finland
[5]Department of Pathology, Turku University Hospital, Turku, Finland
[6]Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland

Background/Objectives: Cell-mediated immune (CMI) response appears to play a considerable role in influencing the outcome of an HPV infection and the failure to develop sufficient CMI can result in persistency and progression of the infection. CD4+ lymphocytes participate in initiating and maintaining immune response, but the role of CD8+ lymphocytes in HPV infection is less clear. Characterization of various T-cell subsets within in CD4+ and CD8+ populations according to immune activation and differentiation could provide more knowledge on the different outcomes of HPV infection.

Methods: A subset of 42 mothers and their children (n=28), from the Finnish Family HPV study, was included in these evaluations. The participants were divided in four groups based on the mothers' genital or oral HPV16 infection status during the six-year follow-up: persistent HPV16 oral and/or genital vs always HPV negative. Peripheral blood mononuclear cells (PBMCs) from previously cryopreserved venous samples were immunophenotyped using 23 markers analyzed in flow cytometry (BD LSRFortessaTM Cell Analyzer). T-cell subpopulations were defined by presence or absence of different cell surface markers to either early or late activated cells, memory or naïve cells and as differentiated or undifferentiated cells. Proportion of the CD4+ or CD8+ lymphocytes by their immunophenotyped subsets were compared between the groups: mothers, children, and mother-child dyads.

Results: The mean rank distribution of CD8+ memory cells (CD45RO+CCR7-CD8+ cell population) was significantly higher among mothers with persistent genital HPV16 infection than in those who were genital HPV16 negative (p=0.048). The median levels of both the antigen presenting CD4+ cells (HLADR+CD3+CD4+) and activated CD8+ cells (CD38+HLADR+CD3+CD8+) were significantly lower in the mothers with the persistent oral HPV16 infection than in those being always oral HPV16 negative ones (p=0.038 and p=0.033). Interestingly, among children significant higher mean levels of activated CD4+, CD8+ cells and circulating CD8+ memory cells were only seen among those whose mother had persistent oral HPV16 (p=0.038, p= 0.008 and p=0.0033, respectively). The mother-child comparisons revealed several statistically significant differences both in CD4+ and CD8+ T-cell subsets and also as related to the mother's HPV status indicating that there is disparity in immunophenotype activation between children and their mothers.

Conclusions: Our results provide tentative evidence that the mother's persistent HPV infection can be associated with changes in peripheral blood T-cell distribution. Furthermore, the mother's HPV infection might result in immune alterations in her offspring, especially the oral infection.

Tian Pu
China

Tian Pu
China

#3726

Mechanism of HPV16 E2 promoting its persistent infection by inhibiting cGAS-STING signaling pathway

05 - Immunology

Background/Objectives: HPV employs multiples strategies to escape immune surveillance. And one important approach is to inhibit DNA sensing pathway in the host cells. Previous studies have confirmed that E6/E7 can inhibit the activation of cGAS-STING signal pathway. However, how HPV can escape immune recognition during its persistent infection without gene integration is unclear. We hypothesized that HPV E2 may impair innate immune recognition of HPV and promot persistent infection.

Methods: To confirm if cGAS-STING signal Pathway can be activate by HPV, HPV16PsV was applied to infect HaCaT and the activation of STING was measured by Western-blot and Immunofluorescence. And we overexpressed E2 in HaCaT by trasfecting HPV16 E2 plasmids to observe whether E2 has an effect on the activation of cGAS-STING signal pathway. Quantitative PCR and western blotting were performed to determine the RNA and protein expressions of STING and its downsream cytokines, respectively.

Results: STING was activated and its expression increased in HaCaT after being infected by HPV16PsV. Compared with the control group, the expression of STING, IRF3 and ISG15 significantly decreased in HaCaT overexpressed HPV16 E2.

Conclusions: HPV16 impairs innate immune detection via reducing STING expression in host cells during its persistent infection without gene integration.

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Tewari Krishnansu
United States

Tewari Krishnansu S
United States

#3208

EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9: RESULTS OF PHASE 3 TRIAL OF CEMIPLIMAB VS INVESTIGATOR'S CHOICE CHEMOTHERAPY IN RECURRENT/METASTATIC CERVICAL CARCINOMA

08 - Immunotherapy - Immuno-oncology - New treatments

Tewari K[1], Monk B[2], Vergote I[3], Miller A[4], De Melo A[5], Kim H[6], Kim Y[7], Samouëlian V[9], Lorusso D[10], Damian F[11], Chang C[12], Gotovkin E[13], Takahashi S[14], Ramone D[15], Pikiel J[16], Guerra Alía E[18], Colombo N[19], Makarova Y[20], Li J[21], Jamil S[21], Jankovic V[21], Chen C[21], Seebach F[21], Lowy I[21], Mathias M[21], Fury M[21]

[1]University of California, Irvine, United states

[2]University of Arizona, Creighton University, Phoenix, United states

[3]Division of Gynecologic Oncology, Department of Gynecology and Obstetrics, University Hospitals KU Leuven, Leuven, Belgium

[4]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, United states

[5]Division of Clinical Research and Technological Development, Brazilian National Cancer Institute, Rio de janeiro, Brazil

[6]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South korea

[7]Department of Obstetrics and Gynecology, Asan Medical Center, University of Ulsan, Seoul, South korea

[8]St Petersburg State Budgetary Institution of Healthcare, St petersburg, Russia

[9]Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM) and Université de Montréal, Montreal, Canada

[10]Department of Women and Child Health, Division of Gynecologic Oncology, Fondazione Policlinico Universitario A Gemelli IRCCS and Department of Life Science and Public Health, Catholic University of Sacred Heart Largo Agostino Gemelli, Rome, Italy

[11]Centro de Pesquisa em Oncologia, Hospital São Lucas, Pontifical Catholic University of Rio Grande do Sul, Porto alegre, Brazil

[12]Department of Obstetrics and Gynecology, Mackay Memorial Hospital and Department of Medicine, Mackay Medical College, Taipei, Taiwan

[13]State Budget Healthcare Institution Ivanovo Regional Oncology Dispensary, Ivanovna, Russia

[14]Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

[15]Department of Clinical Oncology, Barretos Cancer Hospital (Pio XII Foundation), São paulo, Brazil

[16]Department of Oncology, Szpitale Pomorskie, Gdynia, Poland

[17]Department of Gynecologic Oncology, Białostockie Centrum Onkologii, BiaŁostockie, Poland

[18]Department of Medical Oncology, Hospital Ramón y Cajal, Madrid, Spain

[19]Department of Gynecologic Oncology, University of Milan-Bicocca and Istituto Europeo di Oncologia IRCCS, Milan, Italy

[20]State Budgetary Institution of Healthcare, Clinical Oncology Dispensary #1, Krasnodar, Russia

[21]Regeneron Pharmaceuticals, Inc., Tarrytown, United states

[22]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

Background/Objectives: EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 (NCT03257267) is an open-label, randomised (1:1), multicentre, Phase 3 trial of cemiplimab versus investigator's choice (IC) chemotherapy (chemo) in recurrent/metastatic (R/M) cervical cancer that has progressed after first-line platinum-based treatment.

Methods: Patients were enrolled regardless of programmed cell death-ligand 1 (PD-L1) expression; received cemiplimab 350 mg intravenously every 3 weeks or IC chemo (pemetrexed, vinorelbine, gemcitabine, irinotecan or topotecan), up to 96 weeks; and were stratified by histology (squamous cell carcinoma [SCC] versus adenocarcinoma or adenosquamous carcinoma [AC]). Primary endpoint was overall survival (OS), analysed hierarchically in patients with SCC followed by overall population (SCC + AC). Additional endpoints included progression-free survival (PFS), objective response rate (ORR), quality of life (QoL) and safety. Interim analysis was scheduled when 85% events occurred among patients with SCC pts.

Results: 608 patients were randomised: median age was 51.0 years (range, 22.0–87.0); 477 patients had SCC (77.8%), 131 patients had AC (22.2%) histology; and Eastern Cooperative Oncology Group performance status was 0 (46.5%) or 1 (53.5%). Median cemiplimab exposure was 15.2 weeks (range, 1.4–100.7). At interim analysis, median OS favoured cemiplimab versus chemotherapy (total population: 12.0 vs 8.5 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.56–0.84; one-sided P inf0.001; SCC population: 11.1 vs 8.8 months; HR, 0.73; 95% CI, 0.58–0.91; one-sided P=0.003; AC population 13.3 vs 7.0 months; HR, 0.56; 95% CI, 0.36–0.85; nominal one-sided P inf0.005 [not adjusted for multiplicity]. PFS, ORR, in overall and SCC populations, and mean change from baseline QoL in the SCC population, favoured cemiplimab versus chemotherapy. The most common treatment-emergent adverse events (AEs) of any grade for cemiplimab versus IC chemo were anaemia (25.0% vs 44.5%), nausea (18.3% vs 33.4%), fatigue (16.7% vs 15.5%), and vomiting (16.0% vs 23.4%). Discontinuation due to AEs occurred in 8.7% (cemiplimab) and 5.2% (IC chemo) of patients.

Conclusions: Cemiplimab significantly improved OS over single-agent chemo for patients with R/M cervical cancer after first-line treatment regardless of histology and despite not having been selected by PD-L1 status. No new safety signals were observed.

Oaknin Ana
Spain

Monk Bradley J
United States

#3509

IMPACT OF CEMIPLIMAB ON QUALITY OF LIFE, FUNCTIONING AND SYMPTOMS IN PATIENTS WITH RECURRENT/METASTATIC CERVICAL CARCINOMA: RESULTS FROM EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9

08 - Immunotherapy - Immuno-oncology - New treatments

[1]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[2]Arizona Oncology (US Oncology Network) University of Arizona, Phoenix, United states

[3]Creighton University, Omaha, United states

[4]University Hospitals Leuven, Division of Gynecologic Oncology, KU Leuven, Leuven, Belgium

[5]Brazilian National Cancer Institute, Rio de janeiro, Brazil

[6]Asan Medical Center, University of Ulsan, Seoul, South korea

[7]St Petersburg State Budgetary Institution of Healthcare, St petersburg, Russia

[8]Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM) and Université de Montréal, Montréal, Canada

[9]Seoul National University Hospital, Seoul, South korea

[10]State Budget Healthcare Institution Ivanovo Regional Oncology Dispensary, Ivanovo, Russia

[11]Hospital Sao Lucas PUCRS, Porto alegre, Brazil

[12]Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

[13]MacKay Memorial Hospital, Taipei, Taiwan

[14]Department of Obstetrics , Irvine, United states

[15]Patient Centered Endpoints, IQVIA, Amsterdam, Netherlands

[16]Regeneron Pharmaceuticals, Inc, Tarrytown, United states

Background/Objectives: Cemiplimab significantly improved overall survival in patients with recurrent/metastatic (R/M) cervical cancer after first-line (1L) platinum-based chemotherapy (chemo) (NCT03257267; ESMO-VP-2021). We now report patient-reported quality of life (QoL), functioning, and symptoms from the clinical trial.

Methods: Patients with R/M cervical cancer who progressed after 1L chemo were randomised (1:1) to intravenous cemiplimab 350 mg every 3 weeks (N=304) or investigator's choice chemo for up to 96 weeks (N=304). At baseline (BL) and Day 1 of each 6-week treatment cycle (up to 16 cycles), patients were administered the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. Mixed-effects repeated-measures models estimated overall least-squares (LS) mean change from BL for global health status (GHS)/QoL and physical functioning (PF). Results reported for the squamous cell carcinoma (SCC) and the overall (SCC + adenocarcinoma [AC]) populations were formally defined per statistical hierarchy for multiplicity adjustment. Other analyses for QoL were not adjusted for multiplicity, and nominal P values were reported.

Results: BL scores showed moderate to high functioning and low to moderate symptom burden with minimal differences across groups. For SCC, cemiplimab generally maintained GHS/QoL (LS mean change, 1.2 [95% CI -2.0, 4.3] vs -7.3 [95% CI, -11.5, -3.1]; difference, 8.5; one-sided P=0.00025) and PF (LS mean change, 1.0 [95% CI, -1.9, 3.9] vs -7.3 [95% CI, -11.1, -3.6]; difference, 8.4; one-sided P=0.00008) generally worsened scores with chemo. Findings were consistently better than chemo in the overall population. Significant differences in LS mean changes favoured cemiplimab on other functioning and key symptom scales in the overall and SCC populations (two sided nominal P<0.05). A similar trend was observed in the AC population (formal statistical test was not prespecified).

Conclusions: In patients with R/M cervical cancer after first-line treatment, cemiplimab provided significant benefit versus chemo in GHS/QoL and PF, along with other functioning and key symptom scales.

Olkov Ilya
Russia

Kononova Irina
Russia

#3656

LOCAL IMMUNE STATUS RELATED TO SIL: SPECIALITIES AND POSSIBILITIES FOR IMMUNOMODULATION WITH SOLUTIONS TREATED WITH ULTRASOUND CAVITATION.

08 - Immunotherapy - Immuno-oncology - New treatments

Olkov I[1], Kononova I[2]

[1]Social Programs Development Foundation , Moscow, Russia

[2]Chair of obstetrics and gynecology, Russian Pirogov National Medical Research University , Moscow, Russia

Background/Objectives: To evaluate efficiency of immunomodulation in patients with unfavorable clinical course of local immune status of SIL with solutions treated by ultrasound cavitation.

Methods: Molecular-biological examination of vaginal microbiota was performed using immunohistochemical analysis of biopsy with expression of CD3, CD56, CD20, CD138, M-CSF receptors followed by evaluation of treatment efficiency by with peptide solutions treated by ultrasound cavitation in patients with LSIL with possible progression to HSIL using Fotek ultrasound cavitation technique.

Results: HSIL progression is accompanied by the dominance of Lactobacillus iners in combination with Gardnerella v., E. coli, Enterococcus faecalis ($\chi^2 = 3421$ at $p = 0.006$, $\chi^2 = 32.1$ at $p = 0.003$, respectively). HISL is characterized by an increase in the proportion of cells expressing receptors CD20 (1.5%), CD3 (45%), CD138 (in stromal cells) (12%) and a decrease in M-CSF epithelial infiltration ($r = -0.55$ at $p = 0.000$ for CD20 and for $r = -0.50$ at $p = 0.00$ CD3), which led to creation of a mathematical model for predicting neoplasia was. The sensitivity of the method was 75%, specificity - 92.3%, efficiency - 83.7%. Physio medical immunomodulation with peptide solutions treated by ultrasound cavitation was administered to patients with unfavorable prognosis. A 4,5 times reduction in the risk of neoplasia progression was observed.

Conclusions: Physio medical immunomodulation appears to be efficient in prophylactics of LSIL progression in patients with unfavorable clinical course of the disease.

References: 1. Patent for invention "Method for predicting the risk of progression of recurrent cervical intraepithelial neoplasias of low oncogenic risk associated with human papillomavirus infection", registration number: 2020127844 from 08.20.2020. 2. Shmakova N.A. Features of the local immune microenvironment in cervical intraepithelial neoplasia associated with human papillomavirus. / ON. Shmakova, I.N. Kononova, G.N. Chistyakova, I.I. Remizova // Bulletin of SurGU, Medicine. 2020. No. 4 (46). S.68-73. DOI: 10.34822 / 2304-9448-2020-4-68-73 3. I.R. Minniakhmetov, M.V. Zabelin, I.G. Olkov, R.I. Khusainova "Pilot project for cervical cancer screening using HPV testing" Problems in Oncology, Vol. 66, Dec 2020: 618-624