

**EUROGIN 2019
ABSTRACTS**

POSTERS

2 - Epidemiology and natural history

RETROSPECTIVE ANALYSIS OF THE TRACKING OF THE UTERINE CERVIX CANCER ON WOMEN UNDER 25 YEARS OLD, DURING 5 YEARS, MADE IN VALENÇA CITY, STATE OF RIO DE JANEIRO BRAZIL

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Background/Objectives: In Brazil, in 2011, new guidelines on the uterine cervix cancer screening were published, and it was reviewed and republished in 2016. Both point out 25 years as the age to start the screening, based on evidence studies, that show that the incidence of uterine cervix cancer is low under this age. We know, however, that many professionals from the health area don't corroborate with this minimum age and keep taking preventive measures to uterine cervix cancer in this age range. We know that the incidence of low-grade lesion may be higher in this age range, but the incidence of uterine cervix cancer is very low. On this matter, we decided to analyse the results in our city, evaluating the incidence of the precursor disease of the uterine cervix cancer on women under 25 years old that present cytologies classified as low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), carcinoma "in situ" and invasive carcinoma, according to the Bethesda classification, in the city of Valença-Brazil.

Methods: It is a retrospective study performed during 5 years, from March 2012 to March 2017, approaching young adults, from 18 to 25 years old. The research was made by the cytopathology and pathological anatomy lab, accredited and referenced by the Brazilian health system, in the city of Valença-Brazil. The cytologies made in this age range are classified quantitatively and qualitatively in LSIL and HSIL respectively.

Results: 61.115 exams were evaluated, with 11.002 of these patients being under 25 years old (18%). In this age range, under 25 years old, only 92 cases of precursor disease (LSIL and HSIL) were diagnosed, that is, less than 1%.

Conclusions: Our sampling was very significant. With these numbers, we have back up for a more directed orientation for professionals in our city, concerning the importance of following the new guidelines and the non-performance of the screening for the oncotic cytology on women under 25 years old, living in Valença city. This must be followed, regardless of the number of partners or sexarche. We understand that, with the new recommendations, we can avoid a series of iatrogeneses, such as the making of colposcopies, unnecessary biopsies and the making of high-frequency surgeries.

References: National Cancer Institute (INCA); Brazilian guidelines for cervical cancer screening. 2nd edition; Rio de Janeiro-2016. Nayar R, Wilbur D. The Bethesda System for Reporting Cervical Cytology, Definitions, Criteria, and Explanatory Notes. Springer; 2015.

Table 1

Preliminary analysis on the Genetic Diversities of High-risk Human Papillomaviruses in Chinese women

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Background/Objectives: Human papillomaviruses (HPVs) are associated with various types of cancers, especially cervical cancers. Though most of the HPVs can be cleared from human body in around two years without clinical treatments, persistent infections of high-risk types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 could result in cervical cancers[1]. HPV 16 and 18 were most frequently found in cervical cancers around the world[2]. In Asia, besides types 16 and 18, HPV 52 and 58 were frequently identified in female populations[3]. This project aims to explore the genetic diversities of HPVs in China, especially those high-risk types. We combine probe capture and next generation sequencing technology to obtain the HPV genomes in exfoliated cervical cells. Phylogenetic analysis on the HPV genomes will help reveal the spatially specific lineages in China, providing practical guidance to HPV vaccine developments for Chinese population. We also made efforts to establish HPV-positive cohorts for follow-up investigations on the carcinogenic mechanism of HPV-induced cervical cancers.

Methods: Exfoliated cervical cells were obtained from participants in the National Cervical Cancer Screening Program. HPV detections were conducted with BGI SeqHPV Kit. Samples infected with high-risk HPV types were selected for DNA extraction and genomic sequencing. Full-length HPV genomes of 18 types (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 69 and 82) were used to design the HPV probes by MyGenostics. DNA libraries were enriched by hybridization with the HPV probes and the final libraries were applied to 100 cycles of paired-end index sequencing using the BGISEq500 platform. Clean reads that paired-end aligned perfectly to HPV reference genomes were extracted and subject to de novo assembly with SPAdes 3.12.0. Alignments of HPV genomes were conducted with MAFFT v7.427 and manually edited with BioEdit v7.0.5. Only genomes with a length of over 7000 base pairs were preserved for downstream analysis. Phylogenies of HPV genomes were reconstructed with GTR+I+F+G4 model in IQ-TREE, implementing 1000 UFB (Ultrafast Bootstrap) pseudo-replications. Visualization of phylogenies were conducted with ggtree package in R.

Results: In this preliminary study, a total of 1039 samples were sequenced. As some samples failed to yield intact HPV genomes due to poor DNA quality, HPV genomic sequences were obtained from 780 samples. Among these samples, 30.8% (240) of them were infected with more than one HPV types. A total of 799 genomes comprised of 36 HPV types were obtained. Phylogenetic study revealed that most of HPV16 belonged to sublineages A1, A3 and A4, HPV18 mainly belonged to sublineages A1 and A4, HPV52 mainly belonged to sublineage B2, while HPV58 mostly belong to sublineages A1, A2 and A3.

Conclusions: Currently there exists few systematic studies on the genetic diversity of HPVs in Chinese population. This preliminary study gave us a glimpse on the genetic diversities of HPV16, 18, 52 and 58, which were consistent with reports from other groups. Further explorations on the spatial and temporal distributions and genetic dynamics of high-risk HPV types would facilitate the precision prevention and treatment of HPV-induced cervical cancers in Chinese females. Long-term follow-ups with HPV-positive cohorts are also required to track the viral infection dynamics and disease developments to investigate the carcinogenic mechanisms of HPVs.

References: 1. IARC. 2018. <https://monographs.iarc.fr/wp-content/uploads/2018/07/Table4.pdf>. 2. Li, N., et al. International Journal of Cancer. 2011. 128(4):927-935. 3. Bao, Y.P., et al. Int J Gynecol Cancer. 2008. 18(1):71-9.

2 - Epidemiology and natural history

PREVALENCE OF ABNORMAL PAP SMEAR AND DETECTION OF INTRAEPITHELIAL CERVICAL LESIONS IN A POPULATION OF WOMEN WHO PARTICIPATED IN A CAMPAIGN FOR CERVICAL CANCER PREVENTION AT BUENOS AIRES' UNIVERSITY HOSPITAL

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Background/Objectives: Worldwide, 570.000 women are diagnosed with cervical cancer, and 311,000 deaths, occupying the fourth place and main cause of death from cancer in women of developing countries. In Argentina, 4484 new cases of cervical cancer are diagnosed every year, and 2231 of them die (National Cancer Institute, 2018). It is the second most frequent cancer in women between 15 and 44 years old, being among this population the first cause of death from cancer. The age incidence curve shows a rapid growth from women who are 25 years old to the fifth or sixth decade, followed by a steady period and a variable decline. As cervical cancer is a preventable disease, it is highly recommended to have an organized program in which women are invited to participate and derived for treatment if a lesion is detected. **OBJECTIVES** Detect prevalence of PAP Smears ASCUS+, and the prevalence of cervical lesions

Methods: A cross-sectional cohort study among women between 25 and 65 years old (n=1033) who participated in a campaign to prevent cervical cancer at Hospital de Clinicas Jose de San Martin colposcopy unit in March 2019. Cytology was performed in 1002/1033, and in those with PAP ASCUS+, colposcopy and biopsy of abnormal images was performed.

Results: 6/1002 PAP smears were inadequate and excluded from the analysis. We detected ASCUS+ in 23/996 (2.3%): LSIL in 8/996 (0.8%), HSIL in 6/996 (0.6%), AGC 2/996 (0.2%), ASCH 1/996 (0.1%) and ASCUS 6/996 (0.6%). Biopsy of patients with ASCUS+ and colposcopic lesion reported: in patients with PAP ASCUS: LSIL 3 (13%), CIN3 1 (4%); with PAP ASCH: CIN2 1 (4%); with PAP LSIL: LSIL 5 (21.7%); with PAP HSIL: 1a1 1 (4%), CIN3 4 (17.4%); with PAP AGC: Invasive adenocarcinoma P16+ 1 (4%) We did not found colposcopy lesions in ASCUS: 2/6 (33.3%), LSIL 3/8 (37.5%) HSIL 1/6 (16.7%) and AGC 1/2 (50%) with ASCUS+

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#0470

2 - Epidemiology and natural history

The clinical significance and utility of HPV-DNA testing in Korean women with atypical glandular cells in cervical Pap tests: An analysis of 311 cases at a single institution

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Background/Objectives: The aim of this study is to analyze the correlation between clinically significant histologic results and human papillomavirus (HPV) in women with atypical glandular cells (AGC) in Papanicolaou (Pap) test.

Methods: Data were obtained from the database at Asan Medical Center, for women with AGC in the Pap tests from January 2001 to December 2015. Among these women, those who underwent subsequent HPV-DNA testing and histologic examination (cervix or endometrium) within one year, were identified.

Results: There were 311 women with AGC who had both histologic examination and HPV-DNA testing. A total of 111 women (35.7%) was identified as positive for HPV. In the AGC analysis, statistically cervical squamous or glandular lesions were significantly more common in HPV positive group compared to HPV negative group (61.2% vs. 10.5%, $p < 0.001$). In contrast, regardless of age and AGC subtype, endometrial lesions were not associated with HPV infection (8.1% vs. 4.5%, $p = 0.12$). In all age groups, cervical squamous or glandular lesions were statistically significant in HPV positive group compared to HPV negative group. The most common HPV genotypes in women with AGC were HPV 16 (32.2%), followed by HPV 18 (25.5%).

Conclusions: The HPV-DNA testing in women with AGC may be a useful tool for predicting clinically significant cervical lesions (squamous or glandular). On the other hand, it had no significant contribution in predicting endometrial lesions. In conclusion, it is important to evaluate women with AGC in Pap test by individualization, considering HPV status.

#0548

2 - Epidemiology and natural history

HEAD AND NECK CANCER AND CERVICAL CANCER DETECTION IN RUSSIA

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Background/Objectives: Squamous cell carcinoma of the head and neck can be the following localization: oral cavity, oropharynx, or larynx. On average, HPV is found in 25-30% of cases of head and neck cancer. A significant role in the survival of patients with a diagnosis of malignant lesion is played by the stage of detection of the disease. With the active detection of the disease, including using screening methods, the chance of detecting cancer at an earlier stage is significantly increased. Over the past decades, there has been an increase in the incidence of cervical cancer and head and neck cancer in Russia. The aim of our work was to analyze the indicators of active detection of head and neck cancer and cervical cancer in Russia from 2007 to 2018 according to official statistics from the national cancer registry.

Methods: We analyzed retrospective data with diagnostic codes related to cancers of oral cavity, pharynx, larynx, and cervix from the official statistic using the active detection rates and diagnosis stage statistics in 2007-2018 in Russia.

Results: The active detection rates of oral cancer (% of newly diagnosed cases) ranged from 11.3 to 18.7%, of pharynx cancer - from 8.6 to 10.7%, of larynx cancer - from 4.9 to 13.9%. In general, low values of the indicator of active detection of head and neck cancers demonstrate a low activity of detection of pathology during preventive medical examinations, which leads to a high proportion of neglected stages of this cancers (in 2018, 62.0% cancers of the oral cavity, 82.7% cancers of the pharynx and 58.5% of cases laryngeal cancer were detected at stage III-IV). For comparison, the indicator of active detection of cervical cancer increased from 29.5% to 41.8%, which may indicate some improvement in the functioning of the system of preventive and screening examinations, however 32.6% of cases of cervical cancer were detected at stages III-IV.

Conclusions: The introduction of the widest possible use of screening methods in the early diagnosis of HPV-associated malignant lesions, such as head and neck cancer, cervical cancer, is designed to significantly reduce the number of detected diseases in the later stages, and also to reduce the HPV-associated cancers incidence and mortality. Mass HPV vaccination and organized screening is the only way to reach the significantly change in the situation with the increasing incidence of HPV-associated cancers in country.

#0476

4 - Immunology

EPITHELIAL STROMAL CROSS TALK IN HPV/HIV INFECTION

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Background/Objectives: Background: More than 90% of HPV infections clear naturally and some 5% or so end up in cancer. Despite its demonstrated role in carcinogenesis, persistent HPV infection is not sufficient for human cervical cancer development. Current thinking suggests that the epithelium and the adjacent stroma engage in bidirectional cross talk to facilitate HPV infection and HPV associated cancers. During the course of progression, the tumour microenvironment becomes increasingly associated with an immune or inflammatory infiltrate. Currently epithelial stromal interactions defined in HPV biology relate to cancer, but less is known about the biology of cells in low-grade lesions that contain productively replicating HPV. Objectives: Hence, this study seeks to understand the distribution of immunological and inflammatory markers (biomarkers) in pre-invasive stage disease i.e. HPV infection and associated intraepithelial lesions and to then compare and contrast this with invasive stage disease by looking at the expression of a wider multiplex array of biomarkers. We also want to establish whether or not being HIV infected would alter these distributions.

Methods: Methods: This study is designed as a descriptive cross-sectional translational study. Consenting women between the ages of 18 and 55 will be eligible to participate if they are scheduled for a hysterectomy for their own health and have an abnormal Pap smear or are known to have early invasive stage disease. HIV positive women will be included as part of the HIV infected arm. Women will be seen over two visits: first visit to collect endocervical secretions and cells using the Dacron® dry swab and Rovers® Cervex-Brush Combi®, respectively. Secretions collected with the swab will be used to characterise levels of biomarkers. The brush sample will be used for HPV genotyping (cobas® HPV) and liquid based cytology. The second visit will be in theatre when the uterus will be collected to prepare tissue explants (TE). TE comprise epithelium suspended on a bed of stroma. After 24 hours of incubation, supernatants of TE will be harvested and the levels of various biomarkers including chemokines, cytokines, matrix-metalloproteinases and growth factors estimated. Included in the panel will be MMPs 1,2,3,7 and 9; Growth factors EGF, PDGF, VEGF, various FGFs, TGF and HBEGF; interleukins 1A, 1B, 6, and 8; CCLs 2, 3, 6, 20 and 28; CXCLs 1, 2, 3, 5, 12 and 16; and others.

Results: Results: Baseline characteristics of all women will be summarized by study arm and presented as proportions, means with standard deviation or medians with interquartile ranges. Fisher's exact test, unpaired t-test or rank sum test will be used to compare characteristics in the different study arms. Focus will be on describing the distributions of biomarkers per group: Pattern of secretion of biomarkers in the female endocervical ET, comparing: (i) pre-invasive stage and invasive stage disease, (ii) HIV infected and the HIV uninfected in pre-invasive stage disease, (iii) secretions collected with swabs, versus supernatants from ET in pre-invasive stage disease.

Conclusions: Conclusions: As this study will recruit women with HPV infection or HPV associated intraepithelial lesions and invasive stage lesions, it will shed some light on the point at which changes in biomarker levels occur and thus distinguishing pre-invasive from invasive stage disease.

References: References: Spurgeon ME and Lambert PF: Human Papillomavirus and the Stroma: Bidirectional Crosstalk during the Virus Life Cycle and Carcinogenesis: Viruses; 2017 Woodby B, Scott M and Bodily J: The Interaction between Human Papillomaviruses and the Stromal Microenvironment: Prog Mol Biol Trans Sci, 2016 Doorbar J: Model systems of human papillomavirus-associated disease; J Path, 2016

#0639

4 - Immunology

The concentrations of FAS/APO-1 antigen in HeLa cell lines incubated with retinol.

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Background/Objectives: The aim of the study was to evaluate a soluble form of APO-1/Fas antigen in supernatants from HeLa cell line culture after 24 and 72 hours of incubation with selected retinoic acid concentrations.

Methods: HPV18 - positive cell lines were cultivated with All-trans-retinoic acid in concentrations of 1×10^{-6} M/L and 1×10^{-9} M/L. The culture was incubated for 24 and 72 hours. Control culture with 3 μ l of DMSO was incubated under identical conditions. The concentrations of soluble APO-1/Fas antigen in cell culture supernatants were estimated using an ELISA method.

Results: The culture that underwent 72-hour long incubation with retinoic acid proved to be toxic for cells and was excluded from the analysis. The obtained results showed significant decrease of concentrations of soluble APO-1/Fas antigen in supernatants from cell lines incubated with retinal for 24 hours in comparison with the control.

Conclusions: Higher concentrations of soluble APO-1/Fas antigen in supernatants from HeLa cell line without retinol may constitute a protective mechanism of the cells infected with the virus before undergoing Fas/FasL-dependent apoptosis. Lower concentrations of sAPO-1/Fas antigen in the supernatant from HeLa cell culture incubated with retinol may suggest that mechanisms protecting infected cells against Fas/FasL-mediated apoptosis become defective under the influence of retinol. Our studies confirm that vitamin A and its analogs inhibit proliferation of cells associated with HPV infection and suggest promising effects of retinoid therapy in inhibiting the progression of early cervical lesions into cancer.

#0301

5 - HPV prophylactic vaccines

LONG-TERM IMMUNOGENICITY AND EFFECTIVENESS OF THE 9-VALENT HPV (9VHPV) VACCINE IN PREADOLESCENTS AND ADOLESCENTS

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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 girls and boys aged 9-15 years was extended to assess long-term immunogenicity and effectiveness through approximately 10 years after vaccination. Here, we describe the results of a second interim analysis based on approximately 8 years of follow up after vaccination.

Methods: Participants aged 9-15 years receiving three doses of 9vHPV vaccine at Day 1 and Months 2 and 6 were enrolled in the study extension (N=1272 [females, n=971; males, n=301]). Serum was collected at Day 1 and Months 7, 12, 24, 36, 66, and 90 to assess antibody responses. For effectiveness analysis (for participants ≥ 16 years of age), genital swabs were collected (to assess HPV DNA by PCR) and external genital examination (to detect external genital lesions) was conducted every 6 months starting when participants reached 16 years of age. Pap tests were conducted annually for female participants ≥ 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. Specimens were tested by polymerase chain reaction to detect HPV DNA.

Results: Geometric mean antibody titers peaked around Month 7 and gradually decreased through Month 90, consistent with observed immunogenicity profiles in previous 9vHPV vaccine studies. Seropositivity rates remained $>90\%$ through Month 90 for each of the 9vHPV vaccine types. No cases of HPV6/11/16/18/31/33/45/52/58-related high-grade intraepithelial neoplasia or genital warts were observed in the per-protocol population (maximum follow-up: 8.2 years [median 7.6 years] post-Dose 3). Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in females and males in the per-protocol population were low (49.2 and 37.3 per 10,000 person-years, respectively) and within ranges expected in vaccinated cohorts (based on results from previous quadrivalent and 9vHPV vaccine clinical trials).

Conclusions: This interim analysis demonstrates sustained immunogenicity and effectiveness through approximately 7 and 8 years, respectively, post-9vHPV vaccination of girls and boys aged 9-15 years.

#0378

5 - HPV prophylactic vaccines

UNDERSTANDING CONFIDENCE IN HUMAN PAPILLOMAVIRUS VACCINE IN JAPAN: A WEB-BASED QUESTIONNAIRE SURVEY OF MOTHERS, FEMALE ADOLESCENTS, AND HEALTH CARE PROFESSIONALS

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Background/Objectives: Vaccine hesitancy refers to the delayed acceptance or refusal of vaccines despite availability of vaccination services, which is an outcome from loss of vaccine confidence. Confidence is defined as trust in effectiveness and safety of vaccines and the health system in which those are approved and delivered. Successful national immunization program (NIP) is, therefore, supported by solid vaccine confidence. In Japan, HPV vaccines have been commercially available since the end of 2009 and were introduced into the NIP in Apr 2013 to address increased cervical cancer among young women. However, active recommendation for the vaccine was stopped shortly after that. Although age-eligible girls can receive the vaccine at no cost if they voluntarily visit doctors seeking vaccination, the vaccine coverage rate has sharply declined from approximately 70% to less than 1%. It means that young women still have been exposed to the risk of HPV-related cancers that could be prevented. To build an appropriate strategy for improving vaccine confidence and acceptance in Japan, we conducted a survey to assess levels of HPV vaccine confidence and identify the contextual reasons behind vaccine hesitancy in Japan.

Methods: This is a nation-wide cross-sectional web-based survey of 1,600 mothers of HPV-vaccination eligible young girls, 800 female adolescents aged 15 to 19 years, and 860 health care providers (HCPs), including internists, pediatricians and obstetrician/gynecologists.

Results: The survey was conducted in September 2019 and captured data on key elements of vaccine confidence including perception on importance, effectiveness and safety of HPV vaccines, trust of government and reliable sources of information about health issues. Additionally, the target cohorts were assessed as to their motivation and willingness to receive or recommend HPV vaccination together with determinant factors of their intentions and behaviors. For exploratory statistical comparisons across groups, Pearson's Chi-square or Fisher's exact test will be used to test for statistical differences in categorical variables.

Conclusions: Findings from this study may help shaping public policy and communication strategies to improve future vaccine confidence. Additionally, this study may provide clues for the development of effective public health education, communication and advocacy campaigns towards increasing confidence and acceptance of HPV vaccines.

#0441

5 - HPV prophylactic vaccines

IMMUNOGENICITY AND SAFETY OF A 9-VALENT HUMAN PAPILLOMAVIRUS VACCINE IN VIETNAMESE MALES AND FEMALES (9-26 YEARS OF AGE): AN OPEN-LABEL, PHASE 3 TRIAL

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Background/Objectives: The 9-valent human papillomavirus (9vHPV) vaccine is designed to prevent diseases resulting from infection by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. A Phase 3 local registration study was conducted to assess immunogenicity and safety of the 9vHPV vaccine in Vietnamese males and females aged 9 to 26 years.

Methods: In this open-label study (NCT03546842), 9- to 26-year-old Vietnamese males and females received 3 doses of 9vHPV vaccine (Day 1, Month 2, and Month 6). Serum samples were collected on Day 1 and at Month 7 for analysis of HPV antibody responses using a competitive Luminex immunoassay. The primary objective of the study was to demonstrate that following 9vHPV vaccination, the percentage (%) seroconversion at Month 7 for each vaccine HPV type met the pre-specified statistical criteria of a lower limit of 95% confidence interval (CI) for % seroconversion of >90%. Anti-HPV geometric mean titers (GMTs) at Month 7 were also summarized for each vaccine HPV type. Immunogenicity analyses were based on the per-protocol immunogenicity (PPI) population that included participants who completed the 3-dose vaccination regimen, provided serum samples within 21 to 49 days post-Dose 3, were seronegative for the relevant HPV type at Day 1, and had no protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination. Injection-site adverse events (AEs) and systemic AEs were recorded (as a %) from Days 1-15 after any vaccination; serious AEs (SAEs) were recorded throughout the study. Participants who received at least one 9vHPV vaccine dose were included in the safety analyses.

Results: A total of 201 participants (101 participants 9-15 years of age; 100 participants 16-26 years of age; comprising 66 males and 135 females) were enrolled in the trial, of whom 198 completed the 3-dose 9vHPV vaccination regimen. Robust anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 responses were induced, with 100% of participants being seropositive at Month 7 for each HPV type. The lower limit of the 95% CI of the % seroconversion was $\geq 98.0\%$ for each of the vaccine HPV types; therefore, the predefined statistical threshold (lower limit of the 95% CI >90%) for acceptable anti-HPV seroconversion was met. No deaths were reported, and there were no vaccine-related SAEs or discontinuations due to AEs. Approximately half of participants (50.5%) reported ≥ 1 AE (injection-site, 45.0%; systemic, 17.0%). One SAE was reported.

Conclusions: The 9vHPV vaccine was highly immunogenic, with acceptable seropositivity rates in this Vietnamese population. The 9vHPV vaccine was generally well tolerated in this population.

#0559

5 - HPV prophylactic vaccines

HPV VACCINE ACCEPTANCE AMONG WOMEN AGED 25 TO 45 IN SLOVENIA: RESULTS OF THE COHEAHR STUDY

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Background/Objectives: HPV vaccination was introduced into the national vaccination program in Slovenia in the 2009/2010 school year and is at present offered for free for girls attending the 6th grade of primary school. Despite being fully state funded, HPV vaccine coverage rates among Slovenian girls remain around 50%. HPV vaccine is available against payment for other populations (e.g. boys and adults); however, little is known about the acceptance of the HPV vaccine among adult women.

Methods: The study was performed as a part of a multinational, open-label study CoheaHr-WP4 (ClinicalTrials.gov Identifier: NCT02837926), which aims to identify determinants of HPV vaccine acceptability, uptake and compliance as well as programmatic and logistics issues in a participating country offering HPV vaccine as part of a cervical cancer prevention strategy, to middle-aged women attending screening. Eligible women were recruited at two different centers. Participants' knowledge and opinion about HPV vaccine was assessed using an anonymous questionnaire and free of charge HPV vaccination was offered to all participating women aged 25-45.

Results: A total of 607 Slovenian women were included in the study. Of these, 306 (50.4%) agreed to complete the anonymous questionnaire only, whereas 301 (49.6%) also agreed to receive HPV vaccine. The mean age of the participants was 35.5 ± 2.8 years. Majority of women (82.2%) have heard about HPV vaccine prior to the visit; however, vaccinated women had better knowledge about the HPV vaccine than non-vaccinated participants ($p=0.007$). Main reasons for vaccine acceptance were protection against cervical cancer and genital warts (93.4%), severity of HPV-related disease (82.7%), HPV vaccine safety (66.8%), free of charge HPV vaccine (62.8%), recommendation for vaccination (55.5%), and other reasons (3.3%). Reasons for refusal of HPV vaccination included the need for additional information regarding the HPV vaccine (31.4%), concerns about HPV vaccine safety and side effects (29.4%), need for additional consultations (12.1%), concerns about HPV vaccine effectiveness and duration of protection (12.1%), vaccine hesitancy (11.8%), lack of benefits from HPV vaccination (5.2%), lack of time (1.3%), personal advice against HPV vaccination (1.3%), and other reasons (3.6%).

Conclusions: The attitude toward HPV vaccine is mostly positive among Slovenian women. However, lack of information and concerns about HPV vaccine safety were recognized as key factors leading to refusal of HPV vaccination, suggesting policy makers should focus on raising awareness on HPV vaccine.

#0560

5 - HPV prophylactic vaccines

Reasons for participation in a HPV vaccine dose reduction clinical trial in sub-Saharan Africa: Does dose matter?

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Background/Objectives: The DoRIS trial is evaluating and comparing the immunogenicity and safety of different dose regimens for 2 different HPV vaccines in 9-14 year old girls in Mwanza, Tanzania. After school sensitisation meetings, parents were invited to the clinic to provide informed consent. Girls then provided informed assent before being randomly assigned to receive 1, 2 or 3 doses of Gardasil-9® or Cervarix®. Qualitative research explored the motivations for participating in a clinical vaccine trial that involves different vaccine doses, clinic visits, interviews and blood sampling. The study started one year before the national HPV vaccination programme commenced.

Methods: In-depth interviews were conducted, after consent/assent, with a random sample of 13 girls, 12 parents and 6 girl-parent pairs. Interviews were audio-recorded and transcribed, and data were analysed thematically using Nvivo.

Results: Parents often decided about daughters' participation in the trial soon after the sensitisation meeting. The decision was discussed with family members, neighbours and others e.g. doctors. If parents disagreed, fathers usually made the final decision. Girls were normally consulted after the parents had made their decision and joint decision-making only took place with some older daughters. Reasons for daughters' participation in the trial were related to having confidence in scientists and in vaccines controlling diseases, knowing someone with cervical cancer, protection of their child from the disease, financial implications of cervical cancer and free health care and checks during the trial. Randomisation to different numbers of doses was not an issue in the decision to participate. When asked hypothetically about HPV vaccine dose preferences, the main issues raised were related to pain avoidance (one dose considered less painful), altruism (one dose would mean more doses to vaccinate more girls), cost saving (lower travelling costs; fewer lost earnings). Some parents felt that 3 doses were likely to be more efficacious whereas most girls believed 1 dose could be as protective as 3 doses, and that 2 and 3 doses were likely to be similarly protective.

Conclusions: Cervical cancer awareness and health benefits of study enrolment meant parents chose to allow daughters to participate in an HPV vaccine trial of different doses, even if they believed higher number of doses were likely to be more efficacious. If single dose HPV vaccine is found to be efficacious in randomised trials, information to parents and children will need to include explanations on efficacy and benefits of a 1-dose regimen including convenience, reduced costs and fewer injections.

#0215

5 - HPV prophylactic vaccines

CHANGES THE PAST DECADE AFTER THE INTRODUCTION OF THE HUMAN PAPILLOMAVIRUS (HPV) VACCINE IN CERVICAL HPV PREVALENCE AT A YOUTH CLINIC IN STOCKHOLM, SWEDEN

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Background/Objectives: This study aimed to follow the impact of human papillomavirus (HPV) catch-up and vaccination the past decade on the very high cervical HPV-prevalence in women at a youth clinic in central Stockholm. Previously, between 2008-2010, cervical HPV-prevalence (70%) and HPV16 prevalence (34%) were high in non-vaccinated women at a youth clinic in Stockholm. Later, 2013-2015, after the introduction of the quadrivalent-Gardasil HPV-vaccine, HPV16 and HPV6 prevalence had decreased. In this investigation, 10 years after primary sampling, cervical samples were collected from young women at the same youth clinic in Stockholm and HPV-prevalence was examined.

Methods: During 2017 and 2018, 178 cervical swabs, from women aged 15-23 years, were tested for 27 HPV types by a bead-based multiplex method. HPV-prevalence data were then related to vaccination status and age and compared to HPV-prevalence in 615 samples from 2008-2010 and 338 samples from 2013-2015 from the same clinic, and to HPV types in 143 cervical cancer cases during 2003-2008 in Stockholm.

Results: The proportion of vaccinated women increased from 10.7% in 2008-2010 to 82.1% in 2017-2018. The prevalence of all 27 HPVs, all high-risk HPVs (HR-HPVs) and the combined presence of the quadrivalent-Gardasil types HPV16, 18, 6 and 11, was lower in vaccinated compared to unvaccinated women (67.4% vs. 93.3%, $p=0.0031$, 60.1% vs. 86.7%, $p=0.0057$ and 5.8% vs. 26.7%, $p=0.002$ respectively). Furthermore, HPV16 prevalence in non-vaccinated women 2017-2018 was lower than that in 2008-2010 (16.7% and 34.7% respectively, $p=0.0471$) and similar trends were observed for HPV18 and 11. In both vaccinated and non-vaccinated women, the most common non-quadrivalent-Gardasil vaccine HR-HPV types were HPV39, 51, 52, 56 and 59. Together they accounted for around 9.8% of cervical cancer cases in Stockholm during 2003-2008, and their prevalence tended to have increased during 2017-2018 compared to 2008-2010.

Conclusions: Quadrivalent-Gardasil vaccination has decreased HPV-vaccine type prevalence significantly. However, non-vaccine HR-HPV types still remain high in potentially high-risk women at a youth clinic in Stockholm.

#0095

8 - HPV testing

Risk factors for type-specific persistence of human papillomavirus and recurrence of cervical intraepithelial neoplasia after conization

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Background/Objectives: Persistent infection with high-risk human papillomavirus (hrHPV) is the key event in the development of high grade intra-epithelial lesions and cervical cancer. The aim of this study was to investigate the clinicopathologic and type-specific parameters related to the persistence and recurrence of hrHPV and cervical intraepithelial neoplasia (CIN) after conization.

Methods: A retrospective review was performed on 309 women who underwent conization or loop electrosurgical excision procedure (LEEP) at the Korea University Guro Hospital between January 2014 and August 2018. All patients underwent hrHPV testing with genotyping before operation. All patients underwent HPV DNA test using Anyplex™ II HPV 28 detection system (Seegene) and cytology between 3 and 6 months after operation. Follow-up visits occurred after 6 and 12 months and every 12 months thereafter. Associations were assessed by multivariate logistic regression analysis.

Results: HrHPV persistence rate was 41.4% at first follow up visit between 3 and 6 months after conization. Forty-three (89.6%) patients of persistent/recurrent CIN patients showed hrHPV persistence. Preoperative factors including age ($p < 0.05$, OR = 1.037, 95% CI = 1.001 - 1.073), hrHPV load ($p < 0.05$, OR = 2.693, 95% CI = 1.341 - 5.407) and multiple hrHPV infection ($p < 0.001$, OR = 4.885; 95% CI = 2.417 - 9.870) were associated with hrHPV persistence in multivariate analysis. Resection margin status and glandular involvement were not associated with hrHPV persistence. HPV52 (25.5%) and HPV53 (57.6%) showed the significant higher persistence rate, while HPV16 did not show higher persistence rate (15.1%). Among 48 patients who were histologically confirmed persistent/recurrent CIN, 12 patients (25%) showed high-grade lesion. CIN persistence/recurrence frequency did not differ between HPV genotypes. Multivariate analysis demonstrated that menopause ($p = 0.001$, OR = 3.969, 95% CI = 1.733 - 9.088), preoperative and postoperative HPV load ($p < 0.05$, OR = 2.430, 95% CI = 1.135 - 5.202, $p < 0.05$, OR = 5.351, 95% CI = 1.091 - 26.236) and multiple hrHPV infection ($p < 0.05$, OR = 2.345, 95% CI = 1.109 - 4.958) were significantly related to persistent/recurrent CIN following conization.

Conclusions: Postoperative hrHPV persistence as a significant predictor for recurrent/persistent CIN was associated with age, viral load and multiplicity. Preoperative HPV52 and HPV53 positive patients showed higher risk for persistent infection than HPV16. Postoperative high HPV load predicts recurrent CIN more accurately than margin status.

#0793

8 - HPV testing

NOVEL CROSS-PLATFORM HIGH-RISK (HR) HPV NAAT POSITIVE CONTROLS FOR USE IN L1 AND E6/E7 TARGETED NUCLEIC ACID (DNA AND RNA) DETECTION METHODS

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Background/Objectives: HPV genotyping nucleic acid amplification testing (NAAT) is becoming a cornerstone triage method for stratifying the risk related to a probable cancer development in the infected population. However, the transition process from HPV Pap testing to a full NAAT, or to reflex type testing is affected by the lack of proper EQA and quality control (QC) material. Predominant categories of positive samples used by the clinical labs are either plasmids or cell line based preparations. Both types have the major disadvantage of not being fully compliant with the FDA recommendations for QC material to monitor the entire workflow, including nucleic acid extraction, amplification, and detection. The composition of current controls (especially the plasmids) is limiting their use in certain NAAT platforms, such as Transcription Mediated Amplification. In addition, they only share certain characteristics of a patient sample specimen. Most of those controls may not contain enough matrix material to challenge the assay and may not be all-encompassing for DNA, RNA and protein (antigen) detection methods. We showcase a cross-platform compatibility study of a novel hrHPV controls for use in a clinical quality management system, either as EQA or QC samples. The positive samples for hrHPV types 16, 18 and 45 contain all the components normally found in the infected patient specimen such as; the integrated and episomal presence of viral DNA, viral RNA, and proteins, as well as the host epithelial cells and are therefore fully compatible with L1 and E6/E7 NA targeted detection of hrHPV.

Methods: The hrHPV panel (hrHPV types, 16, 18 and 45) performance was evaluated with feasibility studies followed by validation studies in Original Equipment Manufacturer (OEM) and clinical IVD laboratories.

Results: OEM lab validation studies were supported by Roche and BD Life Sciences. Data from participating labs in the American Proficiency Institute's US EQA scheme, part of the hrHPV and the HPV genotyping testing panel, were used for the clinical laboratory validation study. Additional sequencing for the presence of the HPV 16, 18 and 45 genotypes was performed by LOXO GmbH.

Conclusions: Feasibility and validation studies of REDx HPV Positive Controls and EQA Positive samples for hrHPV types, 16, 18 and 45 were performed on Roche, Hologic, BD Life Science, Cepheid and Seegene platforms. The studies showed that the products contain all the diagnostic targets normally found in the infected patient specimen: integrated and episomal viral DNA, viral RNA and host epithelial cells. The hrHPV material formulated in a widely acceptable sample transport medium showed excellent compatibility with a range of hrHPV genotyping platforms based on TMA, qPCR and TOCE-DPO methods of detection of HPV target sequences in E6/E7 or L1 regions. This demonstrates the achievement of developing cross-platform compatible controls for hrHPV detection.

#0132

8 - HPV testing

COMPARISON OF TWO COMMERCIAL HPV TESTING ASSAYS FOR DETECTION OF HIGH-RISK HPV IN HEAD AND NECK FINE-NEEDLE ASPIRATION BIOPSY SPECIMENS

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Background/Objectives: Cobas HPV (Roche Diagnostics, Indianapolis, IN) and Cervista HPV (Hologic Inc., Bedford, MA) are commercially available assays for human papillomavirus (HPV) testing that can be used as off-label HPV tests in fine-needle aspiration (FNA) specimens to determine HPV status in patients with oropharyngeal squamous carcinoma. In this study, we compared the efficacy of detection of HPV16/18 and non-HPV16/18 high-risk HPV types (hr-HPV) in head and neck FNA specimens from patients with head and neck squamous carcinoma. Kristina Dahlstrom, PhD. She is from the Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center. Her email address is kdahlstrom@mdanderson.org Thank you so much for your help!

Methods: We retrospectively searched our institutional databases for patients who underwent head and neck FNA biopsy during the period 2012-2018. HPV testing was performed on the residual FNA cytology specimens identified, predominantly smears. Cobas HPV and Cervista HPV16/18 as well as Cervista HPV HR assays were performed according to the manufacturers' instructions. HPV testing results of Cobas and Cervista HPV assays were compared and descriptive statistics were used to evaluate the clinical efficacy for detecting HPV16/18 and hr-HPV. Linear array HPV genotyping assay (Roche Diagnostics) was used in cases in which the HPV results by the two assays were discrepant.

Results: A total of 69 patients were included in the study, 65men and 4 women. The mean age was 60 years (range 35-80). The concordance between Cobas and Cervista HPV assay results was 95.7% (66/69) with a moderate agreement ($\kappa=0.553$) (Table 1). Cervista HPV showed a higher positivity rate than Cobas HPV (97% vs. 94%). Linear array HPV confirmed HPV negativity cases in 2 of 3 cases with Cobas HPV-/Cervista HPV+ test results. In 3 cases with Cervista HPV16+/Cobas HR+ results, linear array showed HPV35 (Table 2). Cervista HPV assay showed HPV16 cross reaction with HPV33/35 in 4 cases. Cobas showed one case with HPV16 cross reaction with HPV33 (Table 2). Overall, Cobas HPV showed a similar sensitivity (98.5% vs. 100%) but a higher specificity than Cervista HPV (100% vs 50%) in detecting HPV16/18 and non-HPV16/18 hr-HPV.

Conclusions: Our results suggest that the Cobas HPV assay can be used as a valid HPV testing assay in head and neck FNA specimens to determine HPV status in patients with head and neck squamous carcinoma. Cobas HPV is more specific than Cervista HPV for determining HPV16 genotypes. Non-HPV16/18 hr-HPV genotypes in our cohort includes HPV33 and HPV35.

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#0150

8 - HPV testing

DO MULTIPLE VERSUS SINGLE HPV INFECTIONS HAVE A GREATER ONCOGENIC POTENTIAL IN THE ETIOPATHOGENESIS OF CERVICAL INTRAEPITHELIAL LESIONS II +?

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Background/Objectives: Human papillomavirus (HPV) infection is the most important etiopathogenic factor in cervical carcinogenesis. This infection causes over 90% of high grade squamous cervical intraepithelial lesions and over 97% of cervical cancers (1). The distribution of the oncogenic potential of the virus depends on many factors. One of the most significant is geographical tropism. In our country, HPV 16, 56, 33, 58 showed the highest oncogenic potential in this order and only in fifth place is HPV 18. Data from the literature indicate that multiple HPV infection significantly increases their oncogenic potential (2). The aim of the study was to investigate whether multiple infection with multiple different types of HPV increases their oncogenic potential in relation to single infection

Methods: At the Clinic for gynecology and obstetrics Clinical center Niš, starting from January 2017, conducted a prospective study that included all patients who were operated on from cervical intraepithelial lesions II + changes, including invasive cervical cancer. HPV typing by Polymerase Chain Reaction (PCR) method was performed in all subjects at the Institute for public health Niš.

Results: In our study, we were unable to demonstrate that the association of different types of viruses increases their oncogenic potential. With statistical significance ($p < 0.05$) we proved that single HPV infection leads to pathological findings from the group of the most severe changes (cervical intraepithelial lesions III and invasive cervical cancer). In the most severe, invasive changes, the presence of only one type of virus was detected in more than 70%, most commonly HPV 16. The results of the study are summarized in Table 1. Histopathological findings Negative HPV test Positive HPV test on the one type Positive HPV test on the more than two types Cervical intraepithelial lesions II 25 % 25 % 25 % 25 % Cervical intraepithelial lesions III 0 50% 37.5% 12.5% Adenocarcinoma of the cervix 28.6% 57.1% 14.3% 0 Invasive cervical cancer 69.2% 15.4% 15.4% Total 10.71% 49.1% 26.3% 14%

Conclusions: A possible explanation for our results is that simultaneous infection with multiple types of HPV can act in terms of their oncogenic potential synergistically or antagonistically, ie that the simultaneous presence of another HPV type may reduce or increase the oncogenic potential of primary HPV infection.

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#0168

8 - HPV testing

Prevalence of HPV types among women in Vojvodina - Distribution of HPV among healthy population

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Background/Objectives: Infection with HPV is common in sexually active young women and most infections are transient and could be cleared spontaneously without clinical consequences. However, some women with persistent HPV infections are in risk for cervical cancer and its associated precursors. Although cervical cytology screening has dramatically reduced the incidence of cervical carcinoma, HPV-related cervical disease, continues to represent a major burden for health-care systems. In Serbia, current estimation indicates that every year 1327 women are diagnosed with cervical cancer and 551 die from the disease. Cervical cancer ranks as the 4th most frequent cancer among women in Serbia and the 2nd most frequent cancer among women between 15 and 44 years of age. The purpose of this study was to investigate the prevalence and distribution of different HPV genotypes among healthy women of Vojvodina province utilising the HPV Euroarray method, and to estimate the prevalence of cervical infections with 18 HR-HPV and 12 LH-HPV types (according to age and cytological results).

Methods: This study presents organized screening program and includes women from Vojvodina (age ranging women from 18 to 65) as target population. The patients' medical history and Pap smear results were collected and HPV tests were performed in each case. Study group is consisted of 1318 women, where 567 women had normal cytology, 751 women ASCUS (Atypical Squamous Cell of Undetermined Significance). The HPV genotyping assay was performed using the HPV EUROArray test (EUROIMMUN, Luebeck, Germany) following the manufacturer's recommendations.

Results: The overall prevalence of HPV was 47.26% (623/1318). HPV positivity among women with normal cytology was 42.7% (242/567) while in the group of women with ASCUS was 50.8% (381/751). Among women with normal cytology HR HPV types were detected in 55.8%, the LR-HPV were found in 12.8% and the their mixed infections were observed in 30.8% cases. Among women with ASCUS cytology HR HPV types were detected in 65.9%, the LR-HPV in 17.6% and the their mixed infections in 16.5% cases. A total of 30 genotypes were detected among the HPV positive women. Five most prevalent types were 16 (30.6%), 31 (15.0%), 53 (11.7%), 51 (9.1%) and 42 (13.0%). The highest prevalence of HPV among healthy population was detected in women aged 25-34 years (60.8%).

Conclusions: Our study of prevalence and distribution of HPV genotypes in healthy women of Vojvodina, according to cytology and age, provides important baseline data and would be helpful for creating effective HPV screening strategies and developing targeted, protective HPV vaccination program in the Vojvodina region.

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#0184

8 - HPV testing

STUDY OF HPV INFECTIVITY OF WOMEN WITH CERVICAL PATHOLOGIES

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Background/Objectives: HPV infection is one of the most common sexually transmitted diseases. According to WHO, HPV types 16 and 18 are the cause of cervical cancer in 70% of cases. The prevalence of HPV types 16 and 18 was studied in healthy women, patients with concomitant and precancerous diseases of the cervix uteri, also cervical cancer in the female population of Tashkent city.

Methods: A total of 787 (100%) women were examined, of which 79 (10%) women with cervical pathology and 21 (2.7%) healthy women volunteers were identified. Of the patients with cervical pathology (morphologically eroded ectropion, endocervicosis, polyps), 26 (32.9%), with CIN of varying degrees, 19 (24%) patients, patients with cervical cancer - 24 (30.4%). The age of women ranged from 18 to 62 years. The material for the study was smears and biopsies from the cervix. HPV testing by PCR. HPV DNA Detection with Genotyping, High-Risk Types was performed by PCR.

Results: In 26.9% of women with concomitant diseases of the cervix, the presence of oncogenic types of HPV types 16 and 18 was revealed. In patients with CIN, HPV DNA was detected in 73.7% of cases; in patients with cervical cancer, HPV was detected in 95.6% of cases, moreover, in practically healthy women, without visual pathology of the neck, virus carriage was detected in 19% of cases. Patients with concomitant diseases and CIN were subjected to cervical conization by an electrosurgical method with systemic antiviral therapy. Patients were monitored for three years, every 6 months HPV testing of cervical smears was performed. After treatment, HPV DNA was present in 49.9% of smear samples.

Conclusions: Scientific studies have proven that HPV has the ability to eliminate from the human body on its own, however, the results of the study showed that even after local and systemic therapy, HPV can persist in the body, finally lead to the development of invasive cervical cancer.

#0292

8 - HPV testing

Multi-Site Comparative Study of the BD COR™ System and the BD Viper™ LT System Using the BD Onclarity™ HPV Assay

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Background/Objectives: Background: The BD COR™ System* is a high throughput, highly automated modular molecular system. The BD Onclarity™ HPV Assay, is an amplified DNA test that detects all 14 high risk HPV types from cervical specimens collected in BD SurePath™ Preservative Fluid and PreservCyt® Solution** and provides extended genotyping capability. The objective of this study was to assess the agreement between values generated by the BD COR System and the BD Viper LT System when using the BD Onclarity HPV Assay.

Methods: Materials/methods: Three test sites were each provided clinical and contrived panels. The clinical panels were prepared with characterized remnant BD SurePath and PreservCyt clinical samples. Panels were aliquoted using individual clinical samples, pooled samples and negative clinical samples spiked with positive clinical samples. Contrived panels were prepared by spiking cell lines containing integrated HPV genotypes 16, 18, or 45 into HPV negative clinical samples. The positive panels were prepared so that each genotype (16, 18, 45 and 11 other) spanned the detection range of the assay with most of these samples near the limit of detection. These panels were tested on the BD COR System at three locations, two external diagnostic laboratories and internally, at the BD laboratory. Results from the BD Viper LT System served as the study reference. All BD Viper LT testing was performed by the BD lab. Each specimen was tested on both the BD COR and BD Viper LT Systems. The BD SurePath preservative fluid was evaluated using 940 specimens (880 clinical and 60 contrived). The PreservCyt solution was evaluated using 930 specimens (915 clinical and 15 contrived). The overall positive and negative percent agreement between the BD COR and BD Viper LT Systems using the BD Onclarity HPV Assay was determined.

Results: Results: Overall, the positive percent agreement between the BD COR and BD Viper LT Systems for the BD SurePath sample panels was 98.3% and the negative percent agreement was 95.3%. The positive percent agreement between the BD COR and BD Viper LT Systems for the PreservCyt sample panels was 98.6% and the negative percent agreement was 95.9%.

Conclusions: Conclusions: The results generated using the BD Onclarity™ HPV Assay on the BD Viper LTTM System and compared to the results from the BD COR™ System at three distinct sites demonstrated equivalent positive and negative percent agreement. *The BD COR™ System and associated assays are not approved for use in the US. **PreservCyt® Solution are currently not approved for use with the BD Onclarity™ HPV Assay in the US.

#0398

8 - HPV testing

Papilloplex: Development of a stand-alone solution for the screening of High Risk, Low Risk HPV as well as detection of mRNA expression for triage in cervical cancer screening.

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Background/Objectives: Background: Cervical cancer is the third most common cancer in women and is associated with persistent HPV infection. Cervical screening is a power tool for the prevention of the disease. GeneFirst has developed a range of in-vitro diagnostic tests that allow for the simultaneous detection and genotyping of all 14 high risk HPV as well as 17 low risk HPV infections. Additionally, GeneFirst is currently developing a one-tube assay to detect the level of E6/E7 oncogene mRNA expression for the 14 high risk-HPV that could be used to predict the risk of high-grade squamous intraepithelial lesion (HSIL) or cervical intraepithelial neoplasia (CIN) 2 or 3. This project is conducted in collaboration with Hiantis as part of the EU funded programme (Project no 806551). The aim of this pilot study was to determine the correlation between the level of E6/E7 mRNA detected using Papilloplex mRNA detection kit and the cytology of 100 women.

Methods: Material/methods: Cervical samples collected from 100 women and retrieved from the Scottish Biobank were evaluated using the Papilloplex all-HPV and mRNA diagnostic kit after DNA and RNA extraction using Quick DNA/RNA Magbead (Zymo). The extracted samples were tested for the presence of high-risk or low-risk HPV infection at the DNA level. Subsequently the relative level of mRNA (normalized with HRPT1) for each category of samples (no lesion, CIN1, CIN2 and CIN3) was determined.

Results: Results: The preliminary results confirmed that the Papilloplex kit is capable of detecting and differentiating 14 hr-HPV and 17 low-risk HPV at the DNA level. Furthermore, using the Papilloplex mRNA kit, our results showed that women with no cervical lesion do not present any detectable E6/E7 oncogene RNA expression whereas mRNA expression is detected in women that present some lesions with a relative higher expression in CIN3 than in CIN1/CIN2 samples.

Conclusions: Conclusions: Preliminary evaluation of the Papilloplex kits on 100 clinical samples has demonstrated that the Papilloplex all-HPV is successful in genotyping 14 hr-HPV as well as 17 low-risk HPV infection and that the Papilloplex mRNA kit can be used to predict the presence of cervical lesion. Further studies, including external validations, will be conducted to evaluate the performance of the Papilloplex diagnostic assays to confirm the results from this study.

#0453

8 - HPV testing

MULTI-SITE EVALUATION OF THE BD CORTM SYSTEM USING THE BD ONCLARITY™ HPV ASSAY WITH SPECIMENS COLLECTED IN BD SUREPATH™ MEDIA AND PRESERV CYT SOLUTION

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Background/Objectives: Background: The BD CORTM System¹ is a high throughput molecular platform designed to address the pre-analytical challenges of today's clinical laboratory by focusing on efficiency, competitive performance and flexibility. The goal of this study was to assess the reproducibility of results and the variance of Ct scores generated by the BD CORTM System when using the BD Onclarity™ HPV Assay. Reproducibility testing is a method used to assess the degree of agreement between results generated by an instrument or assay.

Methods: Methods: Three test sites were provided panels of pooled clinical samples and contrived samples stored in BD SurePath™ (SP) and PreservCyt®2 (PC) primary vials. Contrived specimens were prepared with cell lines containing integrated HPV genotypes 16, 18, or 45 spiked into negative clinical matrix then into each manufacturers' vial. Spike levels evaluated were negative, high negative, low positives, and moderate positive. The panel of pooled clinical samples were previously screened and known to be negative or positive for HPV 16, 18, 31, 33/58, 45, or 52 at levels close to the clinical cut-off. Each panel consisted of 30 replicates/level and was tested at all sites for a total of 90 replicates/level. All technical staff were blinded to the identity of each panel member. Qualitative results were analyzed by comparing the instrument results to the expected results for each of the clinical and contrived specimens. Variance of the Ct score results were evaluated within run, between run and between sites for the positive panel member described above.

Results: Results: All contrived positive panel members (low and moderate) yielded a positive percent agreement (PPA) of 100%. The pooled clinical negative panel members yielded negative percent agreement (NPA) of 100% and 96.7% for SP and PC respectively. Variance of Ct scores for the pooled clinical positive specimens in SP solution resulted in a mean Ct range from 30.38 to 35.13 with overall Standard Deviation (SD) and Coefficient of Variation (CV) range from 0.72 to 2.25 and 2.38% to 6.95%, respectively. The variance for PC resulted in a mean Ct range from 31.03 to 36.46 with overall SD and CV range from 0.90 to 3.08 and 2.89% to 9.21% respectively. The results for all panels showed acceptable performance.

Conclusions: Conclusions: The results generated with the BD Onclarity™ HPV Assay on the BD CORTM System were highly reproducible between runs and sites for all the HPV genotypes tested. ¹The BD CORTM System and associated assays are not approved for use in the US. ²PreservCyt® Solution is currently not approved for use with the BD Onclarity™ HPV Assay in the US.

#0480

8 - HPV testing

LOW-COST POC FOR THE DETECTION AND GENOTYPING OF HIGH-RISK HPV SUITABLE FOR LOW RESOURCED SETTINGS

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Background/Objectives: Human papillomavirus (HPV) infection is the primary cause of cervical cancer. Screening for HPV infection is now recommended globally as a front-line triage for women and together with the introduction of vaccination programs is having an impact upon cervical cancer rates. In resource limited settings VIA is an accepted standard for screening and while attractive, due to its low cost, performance is variable. VIA is less clinically sensitive than molecular HPV testing and it does not address social or cultural norms.

Methods: QuantuMDx and Global Good Fund set out to design and develop an assay for the detection of 14 high-risk HPV oncotypes, that would run on the Q-POCTM platform and provide affordable genotyping results in less than 40 minutes. The assay must also have sufficient validity and acceptance criteria designed in, to ensure that the results are valid and easily interpretable.

Results: Results: QuantuMDx has developed a platform to address the known issues associated with attempting to provide point-of-care results in a resource limited setting. The Q-POCTM is a battery-powered molecular diagnostics device, which utilizes a disposable inclusive test cassette, offering rapid and low cost nucleic acidic amplification testing. QuantuMDx, working with Global Good Fund, have designed and are developing an HPV assay for the detection of 14 high-risk HPV oncotypes with a specimen and internal process controls. Furthermore, a unique specimen collection kit has been developed, suitable for use by health care providers as well as for self-collection. The collection kit utilizes a swab for either cerviovaginal or cervical sampling and a specimen tube. The user simply inserts the swab into the specimen tube and closes the tube. By closing the tube, the cap is sealed, and the stabilisation buffer is released such that the swab is immersed. The specimen tube then easily interfaces with the test cassette allowing for a controlled amount of the resuspended specimen to transfer into the test cassette. The assay detects HPV-16, -18, -31, -33, -39, -45, -51, -52, -56, -58, -59, -66 and -68, along with the human β -globin gene and a segment of the baculovirus. The prototype assay is currently undergoing an external evaluation study in Peru.

Conclusions: Conclusions: QuantuMDx has developed a transformative system for the detection and genotyping of high-risk HPV. The system provides a solution which is less invasive to women and can offer compatibility with self-collected specimens. It is envisaged that this system, specifically designed for low resource settings and providing a turnaround time conducive to screen and treat could offer a transformative option in the detection of cervical cancer.

#0143

9 - HPV screening

BASIC STUDY OF WHETHER DETECTION OF HPV-DNA IN THE FIRST-VOID URINE IS USEFUL AS A MARKER OF CERVICAL HPV INFECTION

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Background/Objectives: Cervical cancer screening coverage in Japan is about 42.1%, which is low compared to other high income countries. In addition, coverage for young women in their 20-30s, where advanced cervical cancer is common is only about 15%. (Fig.1) Therefore, reducing the risk of cervical cancer in women under the age of 40 is an important public health issue.(Fig.2) The aim of this study was to clarify the relationship between detection results of HPV-DNA in first-void urine and cervical sample results, and to evaluate whether cervical HPV infection can be inferred from the results of HPV-DNA in first-void urine.

Methods: The study period was from April 2016 to July 2019 and include 250 women aged between 20 and 67 years with a median age of 45 years who had an ASC-US cytology result and consented to undergoing both a urine and a doctor collected HPV-DNA test. (Fig.3) After giving a urine sample, a doctor-led cervical sample was taken. Both samples underwent HPV partial genotyping using the COBAS 4800 system. (Fig.4)

Results: The concordance rate (Kappa) of HPV-DNA detection from the first-void and cervical sample was 0.76 with 95% confidence intervals ranging from 0.67 to 0.85 from HPV all group. The HPV 16/18 group had very high concordance 0.95, followed by the HPV all group (0.76) and then the HPV others group (0.75).In all cases in the HPV-positive matched group, the doctor's collected cervical samples and partial genotyping were matched. Sensitivity and specificity were calculated using Logistic Regression to assess HPV infection in the cervix from HPV-DNA detection results in first-void urine. Sensitivity of 0.80 to 0.93 and specificity of 0.93 to 0.99 was calculated. Since 95% confidence intervals (blue dashed lines) were tight, we consider the results to be reliable (Fig.5). Furthermore, compared to cytology, the value is higher than that of CIN2 detection sensitivity (0.64 at our institution) of cytology alone, so we consider detection of HPV-DNA in first-void urine to be adequate.

Conclusions: It is possible to infer cervical infection from HPV-DNA in the first void urine since both urine and doctor samples showed good concordance and it is possible that HPV infection in the cervix can be considered to have a sensitivity and specificity as high as about 0.80 or more from detection results of HPV-DNA in the first void urine. The first-void urine sample collection method can complement the existing sample collection method. The first-void urine is accepted by many women because the collection method is simple and there are few restrictions on sample collection. It may therefore, be a potential strategy to increase screening uptake in never screened women.

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#0263

9 - HPV screening

CAN COLPOSCOPY BE DELAYED FOR HPV POSITIVE WOMEN WITH NORMAL TO LOW RISK CYTOLOGY?

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Background/Objectives: In December 2017 Australia's National Cervical Screening Program changed from 2 yearly cervical cytology testing to 5 yearly HPV testing of women aged 25 - 74 years. The current recommendations are that women who are HPV 16 or 18 positive are referred directly for colposcopy, regardless of liquid based cytology result, and women who are HPV other positive are advised for repeat HPV in 12 months, with referral for colposcopy at that time if ongoing HPV positive. We hypothesize that women who are HPV positive with normal to low grade cytology are being overtreated and could have colposcopy delayed.

Methods: Retrospective cohort study of women referred to a metropolitan Melbourne colposcopy unit with HPV positive and normal, pLSIL or LSIL cytology on cervical screening test. Patient data, colposcopy findings, treatment and pathology results were collated and analysed to determine incidence of invasive cervical carcinoma, high grade dysplasia and overtreatment.

Results: One hundred and ninety-nine women were referred for colposcopy with HPV positive and normal, pLSIL or LSIL cytology on cervical screening test. One hundred and seventy-eight women had colposcopy, of which eighty-nine (50%) underwent biopsy and twenty-four (13.5%) were thought to have high grade dysplasia or adenocarcinoma in-situ (AIS) on colposcopic examination. Two patients underwent cone biopsy after AIS was suspected at colposcopy, at which time invasive adenocarcinoma was confirmed in one and AIS in the other. Giving an incidence of invasive cervical cancer of 0.6%. Twelve patients underwent large loop excision of transformation zone (LLETZ) for high grade dysplasia, three of which were found to have low grade dysplasia on final specimen pathology (25% overtreated). Five patients were still awaiting LLETZ at time of review (July 2019). There was no statistically significant difference in age, smoking status, referral cytology, or referral HPV subtype in those diagnosed with high grade dysplasia or greater compared to those with low grade or no dysplasia.

Conclusions: Current guidelines appear to be resulting in over investigation and overtreatment. Colposcopy is associated with patient morbidity including stress, anxiety, bleeding and pain, as well as future obstetric complications, and economic consequences. Further investigation confirming our results in a large multi-centre prospective trial is warranted.

ACCURACY OF mRNA HPV AND DNA hrHPV TESTS COMPARED IN PAIRS FOR CERVICAL CANCER SCREENING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background/Objectives: DNA hrHPV testing brought to the cervical cancer screening an important contribution with its high sensitivity, in spite of low specificity. mRNA HPV test could be a possible substitute or be associated in an algorithm. Although viewed as a set, HPV kits have different characteristics and they should be compared carefully, applied to the same population. The objective of this systematic review and meta-analysis is to compare the accuracy of DNA hrHPV and mRNA HPV tests, as a set and the mainly diagnostic tools analyzed separately, pairwise, always when applied in the same studies, and compared to a histopathological reference standard.

Methods: Eligible studies were identified by searching the electronic databases for papers published until August 2019. The medical subject headings (MeSH) and text words for the terms "cervical cancer", "CIN", "screening", "DNA hrHPV", and "RNA HPV" were inserted. Meta-analysis was performed with MetaDisc and STATA.

Results: Among the 2,052 studies identified, 157 full texts were read. Forty-one studies were included, with a total of 26,506 patients. In this systematic review, two DNA hrHPV and two mRNA tests were mainly identified: Hybrid Capture 2 (HC2) and COBAS 4800, Aptima and PreTect HPV-Proofer, respectively. Analyzed altogether, DNA hrHPV and mRNA HPV test achieved the sensitivity of 93.7% (95%CI 93.1-94.2) and 80.6% (95%CI 79.6 - 81.6); specificity 43.2% (95%CI 42.5- 43.9) and 65.8% (95%CI 65.1- 66.5); and DOR 10.42 (95%CI 7.06-15.39) and 10.59 (95%CI 8.14-13.77), AUC 0.849 and 0.837, respectively. When comparing HC2 and Aptima, with 15 studies, they had similar sensitivity, of 94.4% (95%CI 93.4-95.3) and 93.4% (95%CI 92.3-94.4); and a small advantage to Aptima in specificity, 50.2% (95%CI 49.1-51.2) and 61.2% (95%CI 60.1-62.2); and DOR 12.93 (95%CI 9.48-17.65) and 14.22 (95%CI 8.98-22.51), AUC was 0.914 and 0.902, respectively. The biggest difference was found in COBAS and PreTect Proofer HPV comparison, with 3 studies: Sensitivity of 95.5% (95%CI 93.2-97.2) and 71.4% (95%CI 66.9- 75.6); specificity of 30.9% (95%CI 27.6- 34.5) and 74.5% (95%CI 71.2- 77.7) and DOR of 17.57 (95%CI 3.00- 102.89) and 9.46 (95%CI 3.61- 24.76), AUC 0.998 and 0.760, respectively. In Aptima versus COBAS analysis and PreTect Proofer HPV versus HC2 analysis, 7 studies were included in each one.

Conclusions: mRNA HPV tests, mainly Aptima assay, can be recommended to primary screening, because it has higher specificity with a small loss of sensitivity than DNA HPV tests and PreTect Proofer HPV would be a better possibility in secondary screening. This result is promising as a means to reduce the over-management in cervical cancer triage.

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#0495

9 - HPV screening

HPV and cervical cancer - screening and vaccination strategies in Romania

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Background/Objectives: Cervical cancer remains one of the most prevalent cancers in women worldwide, ranking 4th, with up to 265.000 deaths being attributed to cervical cancer each year. In the European Union, Romania ranks first for mortality due to cervical cancer.

Methods: The most common sexually transmitted disease, HPV infection, has a particular timeline progression, as the highest risk to contact the infection is in the first 5 years of active sexual life, then decreasing with age. The immune system cleans up and offers immunity to most women infected with high-risk HPV strains, but up to 15% of cases become chronic and can cause precancerous lesions and afterwards cervical cancer. Numerous studies have demonstrated the strong causal link between persistent HPV infection and cervical cancer, 70% of all being linked to HPV strains 16 and 18.

Results: An worldwide effort is taken to reduce and prevent cervical cancer, the main techniques used being screening and HPV vaccination, with the hope of a gradual decrease in morbidity and mortality due to cervical cancer.

Conclusions: The present paper aims to present the national screening and vaccination programs implemented in Romania, and to discuss the impact of them.

#0514

9 - HPV screening

HPVPRO STUDY: COMPARISON OF HPV DETECTION IN CERVICAL AND CERVICOVAGINAL SWABS

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Background/Objectives: The cervical screening program in the Czech Republic is based on cytology with HPV triage. Nevertheless, cytology-based cervical screening should switch to HPV-based cervical screening in the next few years. The implementation of primary HPV screening and increasing cervical screening attendance are a major challenge. The offering of self-sampling to cervical screening non-attenders could increase women's participation as was shown in several European countries. The objective of the HPVPro study was to find out the HPV prevalence in the screening population of Czech women since there are no data for the Czech Republic. The second objective was to compare HPV DNA detection in paired self-sampled cervicovaginal swabs and physician-obtained cervical swabs.

Methods: Cervical swabs were taken by a gynaecologist from 1044 Czech women (age 30-64 years) during the regular screening examination. Cervicovaginal swabs were obtained by self-sampling using digene HC2 collection device, Qiagen (HPVPro1, 544 women) and Evalyn Brush, Rovers Medical Devices (HPVPro2, 500 women). All samples were analysed using Hybrid Capture 2 (HC2, Qiagen) HPV DNA detection method, 500 paired samples from the HPVPro2 study were analysed also using Qiascreen HPV PCR Test (Qiagen). HrHPV positive and discrepant samples were genotyped using PapilloCheck HPV-Screening (Greiner Bio-One).

Results: All samples were suitable for analysis using HC2, Qiascreen failed in 1.4% samples. Hybrid Capture 2 detected hrHPV positivity in 11.2% (117/1044) of cervical swabs and 14.0% (76/544) of cervicovaginal swabs sampled by digene HC2 collection device and 10.4% (52/500) of cervicovaginal swabs sampled by Evalyn Brush. HC2 detected hrHPV positivity in at least one sample in 15.2% (159/1044). Qiascreen detected hrHPV in 9.7% (47/486) of cervical swabs and 10.5% (51/486) of cervicovaginal swabs. Qiascreen detected hrHPV positivity in at least one sample in 11.5% (56/486). Concordance of cervical and cervicovaginal hrHPV positivity was 93% for HC2 and 97.1% for Qiascreen.

Conclusions: HPV prevalence in the screening population of Czech women is between 11% and 15% depending on the used HPV detection method. HPV detection in cervical and cervicovaginal swabs was highly concordant using the PCR-based method. The offering of self-sampling could significantly increase the attendance of Czech women in the cervical screening program.

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#0547

9 - HPV screening

Differences in risk between vaccinated and unvaccinated women against human papillomavirus and herd immunity: towards a personalized screening approach

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Background/Objectives: With increased uptake of the vaccination against human papillomavirus (HPV) oncogenic types and increased herd immunity over time, HPV vaccine will provide protection also for unvaccinated women, depending on the vaccination coverage. The resulting difference in cancer risk will determine the price of universal screening for vaccinated and unvaccinated women, in terms of over- and under-screening and highlight the importance of a personalized screening approach.

Methods: We used STDSIM, a stochastic microsimulation model to investigate the herd immunity progress over time in unvaccinated women. We estimated differences in HPV-prevalence rate and cervical cancer risk between vaccinated and unvaccinated women aged 15 to 64 years of the same cohort. Application of the bivalent and the nonavalent vaccination under different coverages among females alone vs females and males were considered.

Results: Findings from our modelling study suggest that in the steady state situation, which is reached after more than 5 decades under all scenarios, the relative cervical cancer risk for unvaccinated compared to vaccinated women ranged from 1.7 to 10.8, depending on the vaccination strategy. The relative risk was higher in lower vaccine coverages, using the nonavalent vaccine and when vaccinating females only. Unvaccinated women are two to three times more likely to developing cervical cancer even at steady state, compared to vaccinated women, depending on vaccination coverage when females and males are vaccinated with the HPV-2. This risk is eight to 11 times higher when only females are vaccinated with the HPV-9. Steady state is reached after about five decades and, before that, the difference in risk for the disease between the two groups is even larger.

Conclusions: We found notable differences in the risk of developing cervical cancer in unvaccinated compared to vaccinated women under all vaccine coverage assumptions. Since the disease risk is one of the most important variables that determines an optimal screening program, we aim to incentivize thinking towards personalized cervical cancer screening, dependent on the vaccination strategy.

#0083

9 - HPV screening

Application of the self-sampling diagnostic test for evaluation of human papilloma virus in women

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Background/Objectives: Aim of the study was to estimate the prevalence of human papilloma virus (HPV) of high carcinogenic risk (HCR) in women in the Lipetsk region, using a diagnostic test of self-sampling of vaginal discharge for HPV test.

Methods: It examined 455 female residents aged between 21 and 65. The selection of the material for the HPV-HCR study was performed both by the woman herself from the vagina with Qvintip device and by a gynecologist from the cervical canal. The material obtained by the specialist was placed in a test tube of the Eppendorf type with a transport medium; the material selected by the patient alone was placed in a dry test tube according to Qvintip instructions. Samples were studied by PCR in scraping of epithelial cells for the detection of HPV-PCK (16,18,31,33,35,39,45,52,58,59,67). The independent and medical selection of the vaginal discharge for HPV-test was evaluated according to the women's interview on convenience of using this system.

Results: According to the Qvintip-test, 35 women were identified with the results of the test (7.7%), 38 patients (8.4%) were identified with the HPV-HCR detected by the doctor. 320 out of 455 (70.3%) patients preferred the method of self-sampling of the material. The proportion of women who reported preferring to take samples by a doctor was significantly lower- 135 patients - 29.7% ($p < 0.001$).

Conclusions: Thus, for Qvintip device for self-selection of material for testing on HPV-HCR, high diagnostic efficiency, simplicity and convenience in use are characteristic.

#0062

10 - Self-sampling

A cervical cancer screening theory of change using Fuzzy Cognitive Mapping with Inuit women in Nunavik, Northern Quebec, Canada

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Background/Objectives: Among Canadian Inuit, cervical cancer incidence and mortality rates are up to three times higher than the Canadian average. Cervical cancer is highly preventable through regular screening which, in Quebec, is opportunistic and requires physical examination through Papanicolaou "Pap" smear. Since Human Papillomavirus (HPV) is the necessary cause of cervical cancer, HPV testing is a plausible screening alternative. Furthermore, HPV testing by self-sampling addresses several barriers associated with physical examination and access to healthcare. In a participatory research paradigm, we worked with two communities of Nunavik to explore the possible implementation of HPV self-sampling.

Methods: We gathered key community stakeholders to form an Advisory Committee and traveled to the communities to discuss directly with Inuit women. We presented available facts around cervical cancer, HPV and the female anatomy, and used Fuzzy Cognitive Mapping to facilitate the discussions. We conducted a thematic analysis to summarize data, adding links and weights to represent the relationship of each factor on the outcome: screening for cervical cancer.

Results: According to the 27 Inuit women who participated, the most influential factor in using health services was the cultural awareness of the healthcare provider. A significant barrier to screening was the patients' lack of information. The principal vector of change - the factor most likely to influence other factors - was the means of communication between the healthcare provider and the patient: visual communication was told to be the most effective.

Conclusions: From this experience, we were able to initiate a theory of change based on discussions with those who created it. Discussions allow flexibility, by voicing multiple perspectives and incorporating different types of knowledge. There are significant benefits in using participatory methods and tools to better understand the perspectives of patients, one of them being to address their lived needs and concerns when providing health services.

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Fuzzy Cognitive Map

#0257

10 - Self-sampling

Self-sampling for HPV testing in elderly women

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Background/Objectives: In Sweden, where screening ends at the age of 60-64, about 30% of the cervical cancer cases occur in women older than 60. The primary aim was to evaluate whether self-sampling for HPV-testing is suitable for elderly women. The prevalence of HPV and HPV related dysplasia as well as the sensitivity of cytology was also evaluated.

Methods: Self-sampling for HPV was offered to 1500 women aged 60/75 years. Women with positive results had a second HPV test after 5.5 months on average. Those with an HPV positive second test were examined by colposcopy, and biopsy, a sample for liquid based cytology were obtained.

Results: A sample was provided by 59.5% (893/1500) of the invited women. The number of women participating in each group was 60 years 236, 65 years 238, 70 years 223 and 75 years 196 women. The prevalence of HPV was 4.4% (95%CI 3.2-6.0, n=22). The majority of women, 80%, positive in both HPV test, had dysplasia in histology. HPV related dysplasia, was found in 1.8% (16/893) (95%CI 1.1-3.0) and CIN2+ alone was 1.0% (9/893) (95%CI 0.5-2.0). The positive predictive value for CIN2+ was 36.4% (8/22) after the second HPV test. of the 16 women with dysplasia in histology, 13 (81.3%) had a normal cytology.

Conclusions: We found that among women with two HPV positive test there was a high prevalence of CIN diagnosed by histology. The HPV test with repeat testing and histology showed extremely low sensitivity. Self-sampling was well accepted among elderly women, thus self-sampling constitutes a good strategy in cervical cancer prevention in this age group.

#0308

10 - Self-sampling

PERFORMANCE EVALUATION OF INNO-LiPA® HPV GENOTYPING EXTRA II ON FIRST-VOID URINE

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Background/Objectives: Urinary self-sampling for HPV detection offers a non-invasive alternative to clinician-collected cervical samples and has the potential to increase the number of participants in HPV screening programs. During collection, the first void of urine (FVU) contains mucus and debris from exfoliated cervicovaginal cells, and hence contains significantly more HPV than random or midstream urine¹. The INNO-LiPA® HPV Genotyping Extra II assay allows identification of 32 HPV genotypes and excellent performance has been shown using cervical scrapes. Our aim was to develop and verify an HPV DNA extraction protocol using FVU as input sample for the INNO-LiPA® HPV Genotyping Extra II assay and to assess its performance in comparison to cervical samples. Assessment was done through evaluation of (1) the success rate of the assay on FVU samples, and (2) the diagnostic agreement between FVU and cervical samples for high-risk (HR) and possible high-risk (pHR) HPV genotypes.

Methods: A set of 156 paired FVU, collected using a Colli-Pee™ device with UCM-preservative (Novosanis NV, Belgium), and cervical samples were collected from women referred to colposcopy between 2017-2019 and were stored at -20°C until analysis. HPV DNA reference results were available for both urine and cervical samples (based on another commercially available genotyping method). DNA from FVU and cervical samples was extracted using the QIAamp DNA mini kit (modified protocol using 200 µL sample and final elution of 50 µL) and the QIAamp Media Elute kit (modified protocol as described in IFU of AMP Kit) respectively. The extracted DNA was subjected to INNO-LiPA® HPV Genotyping Extra II assay, according to the manufacturer's instructions.

Results: Valid LiPA results were obtained for all UCM-preserved FVU samples with known reference data, resulting in an overall success rate of 100%. The diagnostic agreement of INNO-LiPA® HPV Genotyping Extra II on paired FVU and cervical samples for HR and pHR HPV genotypes was >90%. A slightly higher number of HPV genotypes was identified in FVU compared to cervical samples.

Conclusions: Performance of the INNO-LiPA® HPV Genotyping Extra II assay using self-sampled FVU was evaluated and demonstrates high concordance with the HPV genotyping results obtained with the paired cervical samples. Hence, non-invasive FVU self-sampling, in combination with the INNO-LiPA® HPV Genotyping Extra II assay, offers a promising alternative to clinician-collected cervical samples for HPV detection and genotyping.

References: [1. Pathak, N. et al. (2014). Accuracy of urinary human papillomavirus testing for presence of cervical HPV: systematic review and meta-analysis. BMJ.]

#0408

10 - Self-sampling

EVALUATION OF HPV TESTING WITH PAPILOCHECK® ON FLOQSWABS® SELF-COLLECTED SAMPLES

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Background/Objectives: Cytology-based testing has been used for cervical cancer screening, but lately there is a shift towards the use of HPV DNA molecular testing and self-collection in both high and low-income countries. The implementation of self-collected vaginal samples for HPV screening supports early detection of cervical cancer, therefore the objective of this study was to assess the performance of the PapilloCheck® HPV genotyping assay using FLOQSwabs® home self-collected vaginal samples.

Methods: 51 home self-collected vaginal samples using FLOQSwabs® (Copan Italia Spa), were obtained, after signing an informed consent, from women attending the company health clinic. Swab samples collected during a 3 week-time frame were stored dry at room temperature and were sent from Italy to Greiner Bio-One in Austria for HPV testing with the HPV genotyping assay PapilloCheck® (Greiner Bio-One GmbH). Upon arrival in Austria, blinded samples were eluted in 5 mL of PapilloCheck® Collection Kit transport medium and subsequently nucleic acids were extracted from 250 µL of each sample and were analysed with the PapilloCheck®, a microarray-based test for the detection and identification of 18 hr HPV and 6 lr HPV types, based on the detection, amplification, and genotyping of a 350 bp fragment of the viral E1 gene.

Results: Out of 51 self-collected vaginal samples, 49 samples showed valid test results, 2 samples were invalid, but valid results were obtained after repeat testing. HPV (hr or lr) was detected in 13 samples (25.5%) and 38 (74.5%) were HPV negative. In the 13 HPV positive samples, 5 were lr and 8 hr, (3 had only one genotype and 4 had multiple genotypes). Detected hr types included HPV 16,18, 31, 58, and 68 genotypes.

Conclusions: Good results were obtained when testing FLOQSwabs® vaginal self-collected samples with the PapilloCheck® HPV genotyping assay. Further improvement of the Papillocheck® test protocol by reducing the sample's elution buffer volume is ongoing, which aims to eliminate invalid results and increases the sensitivity when testing self-collected samples prone to collection variability. Data obtained in this study, still in progress, indicates that FLOQSwabs® vaginal self-collected samples in combination with the PapilloCheck® HPV genotyping assay can be used for HPV screening programs.

#0442

10 - Self-sampling

Women attending routine screening who test Hr-HPV negative on a self sample are at very low risk of disease over 5 years; lessons from the PaVDaG cohort.

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Background/Objectives: Self-sampling is becoming increasingly important and accessible route to engage women in cervical screening. It can be a "game changer" for the populations with poor access to health facilities and and/or poor compliance to screening. We previously conducted cross-sectional study PaVDaG, which demonstrated that a clinically validated PCR-based Hr-HPV test using self-collected vaginal samples showed equivalence accuracy to clinician-taken LBC samples for detection of Cervical Intraepithelial Neoplasia grade 2 or worse (CIN2+) in women who attended for screening over a single episode. We now present a 5 years follow-up of the PaVDaG cohort.

Methods: The primary outcome was the risk of CIN2+ and CIN3+ in women who tested Hr-HPV negative on self-sampling at baseline and for up-to 69 months later. In addition, we estimated the cumulative incidence rate (CIR) for CIN2+ and CIN3+ by Hr-HPV, LBC at a threshold of borderline abnormality and above (LBC≥BNA), HPV16/18 positivity results and by a combination of Hr-HPV Other status and LBC≥BNA results.

Results: The total of 4,528 women who participated in PaVDaG study had Hr-HPV results on self-sampling and completed two rounds of screening. The NPV for CIN3+ of Hr-HPV, HPV16/18 and LBC≥BNA testing were 99.9% (99.7-100), 99.4% (99.1-99.6) and 99.6% (99.3-99.7) at baseline and 99.8% (99.5-99.9), 99.2% (98.8-99.4), and 99.3% (99.0-99.5) for up to 69 months later. Similar NPVs were observed when CIN2+ was used as an outcome. Five-years CIR for CIN2+ and CIN3+ of self-sampled Hr-HPV positive (Hr-HPV+) women was 19.6% (16.9-22.5) and 11% (8.9-13.4) respectively compare to 44.3% (38.4-51.3) and 25.7% (20.6-32.0) for women who had LBC≥BNA at base line. The highest five-years CIRs for CIN2+ and CIN3+ of 70.2% (61.1-80.7) and 46.4% (36.9-58.4) were associated with women who were HPV 16/18+ and LBC+. Five-years CIR for CIN2+ and CIN3+ of self-sampled HPV Other+ women who had negative LBC was 3.8% (2.3-6.3) and 2.4% (1.3-4.6) respectively.

Conclusions: The risk of CIN2+ and CIN3+ in self-sampled Hr-HPV negative women was below 0.6% and 0.2% respectively for up-to 69 months after baseline testing. This supports the credibility of a five-year screening interval in women who test Hr-HPV negative on a self sample.

#0445

10 - Self-sampling

Standardized and volumetric collection of first-void urine for detection of STIs and HPV: A comparison between Colli-Pee® and a standard urine cup

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Background/Objectives: A properly collected first-void urine sample is vital for accurate detection of sexually transmitted infections (STIs) and Human Papillomavirus (HPV). The aim of this study was to evaluate the accuracy in volume of first-void urine collected using Colli-Pee® FV-5000, a first-void urine capturing device as well as compare the collected volume with a standard urine cup.

Methods: A total of 563 participants were included in three studies. Each donor was asked to collect a first-void urine sample, not having urinated 1 to 2 hours prior to collection, using one of the Colli-Pee® device variants (20ml or 10 ml). The participants also collected a second first-void urine sample of 20ml using a standard urine cup. A total of 443 samples were obtained. The volume of the sample collected was calculated by: (1) Subtracting the total weight of the collected sample plus collection device by the weight of an empty collection device or (2) Pipetting the sample volume from the tube.

Results: Four participants likely did not complete the collection using the Colli-Pee® device since the collected volume was lower than the initial buffer solution. These participants were seen as outliers and excluded from analysis, giving a total of 559 samples collected with Colli-Pee®. The volume of sample collected with Colli-Pee® was consistently around the targeted volume of the collector tube: (a) 20ml variant - Average volume collected: 19.66ml ($\sigma=1.83$) and (b) 10ml variant - Average volume collected: 10.0ml ($\sigma=0.89$ ml). The volume collected with a standard urine cup was consistently above the targeted 20ml volume: Average volume collected: 23.03ml ($\sigma=13.48$ ml). For further analysis, by setting the acceptance range of the captured volume to 18-22ml and 9-11ml, the results show a significant difference (Pearson Chi-Square, $p<0.005$) between the collection methods. For Colli-Pee® 20ml and 10ml respectively, 84.8% and 89.4% of the collected samples are within this specified range, while only 15.1% of the samples collected with a standard urine cup fall in this range. There is also a significant difference (Fisher's Exact Test, $p<0.005$) for samples that fall out of this specified range, with 82.3% coming from samples collected using a standard urine cup, while only 17.7% from those collected using the Colli-Pee®.

Conclusions: The Colli-Pee® device allows for more accurate and volumetric collection of first-void urine (20ml or 10ml) compared to a standard urine cup.

#0524

10 - Self-sampling

Acceptability and Accuracy of Cervical Cancer Screening Using a Self-Collected Veil for HPV DNA Testing by Multiplex Real-Time PCR among Adult Women in sub-Saharan Africa

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Background/Objectives: Cervical cancer is caused by high-risk Human papillomavirus (HR-HPV) infection. Self-collection of genital specimens and HPV DNA testing are methods increasing screening rates. The cross-sectional GYNAUTO-CHAD study compared the acceptability and HPV DNA diagnostic accuracy of clinician-collected endocervical sample with swab (as reference collection) and genital self-collection method with veil (V-Veil-Up Gyn Collection Device, V-Veil-Up Pharma Ltd., Nicosia, Cyprus) in adult women living in N'Djamena, Chad, recruited from the community.

Methods: Five of the 10 districts of N'Djamena were randomly selected for inclusion. Peer educators contacted adult women in community-churches or women association networks to participate to the survey and to come to the clinic for women's sexual health "La Renaissance Plus". A clinician performed a pelvic examination and obtained an endocervical specimen using flocked swab. Genital secretions were also obtained by self-collection using veil. Both clinician- and self-collected specimens were tested for HPV and HR-HPV DNA using AnyplexTM II HPV28 genotyping test (Seegene, Seoul, South Korea). Acceptability of both collection methods was assessed; test positivities were compared by assessing methods agreement, sensitivity and specificity.

Results: A total of 253 women (mean age, 35.0 years) were prospectively enrolled. The prevalence of HPV infection was 22.9%, including 68.9% of HR-HPV infection (HR-HPV prevalence: 15.8%, 95%CI: 11.3-20.3), with unusual HR-HPV genotypes distribution and preponderance ($\approx 70\%$) of HR-HPV targeted by Gardasil-9[®] vaccine. Veil-based genital self-collection showed high acceptability (96%), feasibility and satisfaction. Self-collection by veil was non-inferior to clinician-based collection for HR-HPV DNA molecular testing, with "good" agreement between both methods, high sensitivity (95.0%; 95%CI: 88.3-100.0%) and specificity (88.2%; 95%CI: 83.9-92.6%). Remarkably, the rates of HPV DNA and HR-HPV DNA positivity were significantly higher (1.67- and 1.57- fold, respectively) when using veil-based collected genital secretions than clinician-collected cervical secretions by swab.

Conclusions: These observations highlight the unsuspected high burden of cervical oncogenic HR-HPV infection in Chadian women. Self-collection of genital secretions using the V-Veil-Up Gyn Collection Device constitutes a simple, highly acceptable and powerful tool to collect genital secretions for further molecular testing and screening of oncogenic HR-HPV that could be easily implemented in the national cervical cancer prevention program in Chad.

#0169

11 - Genotyping

Evaluation of p16/Ki-67 Dual Staining Compared with HPV Genotyping in Anal Cytology with Diagnosis of ASC-US for Detection of High-Grade Anal Intraepithelial Lesions

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Background/Objectives: Human Papillomavirus (HPV) infection is the main risk factor for anogenital cancer. The objective of this study was to compare p16/Ki-67 dual staining to HPV genotyping in anal cytology samples with an atypical squamous cell of undetermined significance (ASC-US) for the identification of high-grade squamous intraepithelial lesion (HSIL).

Methods: Anal cytology samples with an ASC-US result (n = 111) were collected from patients of a university hospital (Lyon, France) from 2014 to 2015. Cases with remaining squamous cells (n = 82) were stained using p16/Ki-67 dual staining (CINtec-Plus kit) and analyzed for HPV screening (CLART2-PCR kit) using a composite endpoint of biopsy and cytology results on follow-up specimens.

Results: Detection of HSIL on follow-up specimens (5/22 biopsies; 1/29 cytology samples) was obtained in two out of six cases with p16/Ki-67 versus five out of six with HPV genotyping alone. Sensitivity and specificity to detect HSIL for p16/Ki-67 was 33% (95% confidence interval [CI] [4; 77]) and 49% (95%CI [34; 64]) versus 83% (95%CI [36; 99.6]) and 13% (95%CI [5; 27]) for HPV genotyping. p16/Ki-67 dual staining and HPV genotyping in anal cytology with a diagnosis of ASC-US and the diagnosis on follow-up specimens

Follow-up specimens	P16/Ki67 + (%)	HR-HPV + (%)	Biopsy	Normal
(n=1)	0 (0)	1 (100)	HSIL (n=5)	1 (20)
			LSIL (n=16)	9 (56.2)
			Cytology	3 (30)
			NILM (n=10)	6 (60)
			HSIL (n=1)	1 (100)
			LSIL (n=6)	5 (83.3)
			ASC-H (n=6)	2 (33.3)
			ASC-US (n=6)	4 (66.6)
			Total (n=51)	25 (34)

HPV-HR=High-risk human papilloma virus; HSIL=High-grade squamous intraepithelial lesions; LSIL=Low-grade squamous intraepithelial lesions; ASC-H=Atypical squamous cell - cannot exclude high grade lesions; ASC-US=Atypical squamous cell of undetermined significance

Conclusions: HPV genotyping was more sensitive but less specific than p16/Ki-67 staining for the detection of subsequent HSIL in ASC-US anal cytology. A larger study is required to evaluate the combination of these biomarkers for triage

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#0326

11 - Genotyping

Genotyping of human papillomavirus (HPV) in a healthy patient population and in patients with suspected cervical intraepithelial neoplasia.

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Background/Objectives: Human papillomavirus infection - HPV is one of the most common sexually transmitted infections worldwide. Persistent infection with highly oncogenic HPV types can lead to a significant percentage of HSIL lesions and consequently to cervical cancer. Long-term infection with highly oncogenic HPV types is a significant health problem in the female population. The vaccination programs introduced against human papillomavirus may significantly affect the epidemiological situation and the prevalence of specific virus genotypes. Aim: Analysis of the results of human papillomavirus genotyping in a healthy patient population and in patients with suspected cervical precancerous changes.

Methods: The analysis included 188 patients who were registered to Specialist Medical Practice to perform a preventive supplementary test for human papillomavirus infection or due to an abnormal cytological examination according to The Bethesda System. The aim of the study was to exclude or confirm the process of active HPV infection and cervical pathology. All patients diagnosed with abnormal cytology, HPV 16 or 18 infection and clinically suspected cervical image underwent colposcopy and targeted biopsy of suspected sites. In case of unsatisfactory colposcopy, cervical canal curettage was performed. The material for molecular diagnostics was collected with a combi brush from the ectocervix, endocervix and vaginal fornices. The collected material was subjected to further molecular processing in an independent, standardized molecular diagnostics laboratory. The study was performed by PCR and nucleic acid hybridization. The test detected DNA of 37 HPV genotypes - including: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39 and CP6108.

Results: In the group of women under 25 years old, HPV positive patients constituted over 70% of the population, while in the group from 26 to 40 years old 57%, respectively. The percentage of positive results in the group over 41 years old was only 25% - the smallest studied group. The most frequently detected HPV types in the entire study group included: - HPV 16 - 13%, - HPV 52 - 9%, - HPV 53 - 8%, - HPV 6 - 6% - low oncogenic type, - HPV 31 - 6%. In the group up to the age of 25, the most frequently detected types of HPV included: - HPV 52 - 11%, - HPV 16 - 9%, - HPV 51 - 6%, - HPV 6 - 6% - low oncogenic type, - HPV 54 - 6% - low oncogenic type. In the group up to the age of 40, the most frequently detected HPV types included: - HPV 16 - 17%, - HPV 52 - 8%, - HPV 53 - 9%, - HPV 6 - 7% - low oncogenic type, - HPV 31 - 6%. In the group over 41 years of age, the most frequently detected HPV types included: - HPV 52 - 13%, - HPV 62 - 13% - low oncogenic type.

Conclusions: In the studied population of patients, mainly residents of the Wielkopolska Province and Poznań, agglomeration, we observe a significant decrease in the prevalence of HPV 16 genotypes, especially HPV 18 in favor of highly oncogenic HPV 51,52,53 types. Such changes are probably related to the primary prevention program, namely the HPV vaccination program introduced by local authorities approximately ten years ago.

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#0359

11 - Genotyping

PREVALENCE OF SEXUALLY TRANSMITTED INFECTIONS AMONG WOMEN LIVING IN REMOTE AREAS ALONG THE AMAZON RIVERS - BRAZIL

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Background/Objectives: Sexually transmitted infections (STIs) are among the most common acute conditions causing considerable morbidity worldwide, especially among women of child bearing age. The World Health Organization (WHO) estimates that more than one million cases of sexually transmitted infections (STIs) are acquired every day with chlamydia, gonorrhea, syphilis, and trichomonas infections being the most prevalent. Many STIs are often asymptomatic and can therefore go undetected for long time periods. If left untreated, some STIs can lead to serious consequences in the female reproductive tract, including the development of pelvic inflammatory disease (PID), ectopic pregnancy, infertility and cancer. In Brazil, the Ministry of Health states that women between 25 and 39 years are the most susceptible to get STIs. The data is however restricted to HIV/AIDS, hepatitis and syphilis while studies addressing the prevalence of other STIs are still scarce. Here, the prevalence of 11 STIs were determined among women living in isolated riverine communities, without adequate access to vaccinations and basic health care, in the Amazon region of Brazil.

Methods: Cervical samples were collected in 2017 and 2018 for direct detection of 11 STIs; *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HSV 1, HSV 2, *Haemophilus ducreyi*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Treponema pallidum*, *Trichomonas vaginalis*, *Ureaplasma parvum* and *Ureaplasma urealyticum* using a DNA microarray test system (EuroimmunTM). The project was approved by the Ethics Committee of Santo Amaro University, São Paulo, Brazil. (Brazilian Platform - CAAE: 61414216.4.0000.0081).

Results: From the 200 cervical samples analyzed by the Microarray method, 67% (n=134) were infected with sexually transmitted agents as following: 51.5% of the samples with *Ureaplasma parvum*, 31.5% with *Mycoplasma hominis*, 14.5% with *Trichomonas vaginalis*, 8.5% with *Ureaplasma urealyticum*, 2% with *Chlamydia trachomatis* and *Mycoplasma genitalium*. Herpes simplex virus Type 1 and Type 2 infection occur only in 1% of the samples and *Treponema pallidum* in 0.5%. 17.5% (n=35) of the samples had high and low risk oncogenic Human Papillomavirus infection, of which 85.7% of the samples were associated with infection by STI agents.

Conclusions: The study indicates the importance of STI prevention in isolated populations, since the occurrence of these processes may be a facilitating factor for the occurrence of HPV infection and cervical cancer.

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#0438

11 - Genotyping

EVOLUTIVE PREVALENCE OF DIFFERENT HUMAN PAPILLOMAVIRUS GENOTYPES FROM UTERI CERVIX SMEARS IN FRANCE : A REGIONAL EXPERIENCE OF A LABORATORY USING THE CLART® HPV TEST (GENOMICA - MADRID - SPAIN) BETWEEN 2014 AND 2018.

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Background/Objectives: Human Papilloma Virus (HPV) is the necessary cause of cervical cancer and HPV infections represent the most common sexually transmitted diseases affecting millions of people in the world. Particularly HPV 16 and 18 have been detected in about 70% of uteri cervix cancer worldwide. The authors studied the prevalence evolution of 33 HPV types during 5 years from cervical smears analyzed in the same French laboratory in 2014 and 2018.

Methods: All cervical swabs were collected in SurePath™ preservative fluid (BD, San Jose, USA) and 33 HPV genotypes were searched by using the CLART® HPV test (Genomica, Madrid, Spain). 455 cervical swabs from women aged 20 to 85 years were tested in 2014 and 524 cervical swabs from women aged 19 to 81 years in 2018. HPV prevalence data in 2014 and 2018 were then compared using Chi-square analysis for all patients and for three different age groups: under 30 years, between 30 and 50 years and over 50 years. Moreover the authors compared the HPV prevalence with cervical cytology classes (Bethesda 2014) and patients vaccination status.

Results: Total cervical HPV prevalence was 56% (256/455) in 2014 and 60% (314/524) in 2018. Considering all patients together, the genotype repartition was significantly different between 2014 and 2018 and the five most common high risk HPV types detected in 2014 were HPV16 (17.1%), HPV52 (9.01%), HPV31 (6.1%), HPV53 (5.05%) and HPV51 (4.4%) and in 2018 were HPV16 (10%), HPV53 (7%), HPV31 (6.8%), HPV52 (5.5%) and HPV58 (5.5%). The genotype repartition was also significantly different between 2014 and 2018 in the group of women aged 30 to 50 years.

Conclusions: The differences of HPV types prevalence in 2014 and 2018, highlighted an evolution in the frequency of some HPV oncogenic strains. Several factors could explain these variations, among these, probably the patients vaccination status which increased progressively in France during the last years.

11 - Genotyping

TYPE DISTRIBUTION OF HUMAN PAPILLOMAVIRUSES IN PREMALIGNANT LESION AND INVASIVE CARCINOMA OF CERVIX IN KOREA

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Background/Objectives: To date, more than fifty human papillomavirus (HPV) genotypes have been identified in the female reproductive tract, and certain HPV types cause invasive cervical cancer. There are some studies about the prevalence of HPV infection in premalignant lesion. In Korea, however, the study for large population has not been sufficiently published. The primary objective of this study was to evaluate the frequency of HPV types in different grade of cervical intraepithelial neoplasia (CIN), squamous cell carcinoma (SCC), and adenocarcinoma (ADC) of cervix confirmed by loop electrosurgical excision procedure (LEEP) biopsy in Korean women. The secondary objective of this study was to identify which types of HPV were associated with negative LEEP results despite of positive preconization cytology.

Methods: We conducted retrospective analysis of 2162 patients who underwent LEEP in the Asan medical center from 2007 to 2014. Preconization clinical characteristics, as well as HPV status, were reviewed. Comparisons of frequency distributions were analyzed using Chi-squared Test. P-values less than 0.05 were considered to indicate a significant difference. Data were analyzed using SPSS(version 20.0; SPSS Inc., Chicago, IL).

Results: The median age was 41 years, and 77.9% of patients were premenopausal women. Histologic results of LEEP showed 41.2% of cases were CIN III, 27.2% were chronic cervicitis, 10.4% were CIN I, 8.6% were CIN II, 5.9% were invasive SCC, 4.2% were normal, 1.4% were invasive ADC, and 1.1% were adenocarcinoma in situ (AIS). Among the study population, 85.7%(N=1853) of patients were positive for HPV. The top five HPV types were HPV 16, 53, 58, 18 and 56 in CIN I, those in CIN II were HPV 16, 58, 18, 52, and 35, and those in CIN III were HPV 16, 58, 33, 52, 31. For most common type of HPV infection, HPV 16, 18, and 33, and HPV 18, 16, and 52 were identified in invasive SCC, and in ADC, respectively (table 1). In 1168 patients with ASC-H or worse cytologic results, 270 patients revealed negative LEEP biopsy such as no abnormal findings and chronic cervicitis, and 898 patients revealed CIN I, II, III, invasive SCC, and ADC. The prevalence of HPV 16 and 58 significantly decreased, and that of HPV 70 significantly increased in negative LEEP biopsy group (table 2).

Conclusions: Among the study population, the most common type of HPV was HPV 16, and the prevalence of HPV 16 increased with increasing grade of CIN. HPV 18 is more dominant than HPV 16 in ADC. These results were consistent previous studies in other countries. In the patients with ASC-H or worse pap results, the low prevalence of HPV 16 and 58, and the high prevalence of HPV 70 were associated with negative LEEP results.

#0074

12 - Molecular markers

PERFORMANCE OF p16/KI67 IMMUNOSTAINING AS A SCREENING TOOL FOR COLPOSCOPY IN WOMEN PRESENTING WITH LOW GRADE INTRAEPITHELIAL LESION AT CERVICAL CYTOLOGY

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Background/Objectives: Low grade intraepithelial lesion (LSIL) at cervical cytology is a common reason for colposcopy referral. The purpose of this study was to evaluate the value of p16/Ki67 immunostaining in triaging women with LSIL for colposcopy.

Methods: We conducted a prospective study including all women aged 25 years or more with LSIL referred to our unit. Women with previous treatments for cervical lesions were excluded, as well as women who were tested with cytology plus HPV DNA assay. p16/Ki67 immunostaining was performed: a positive case was followed by immediate colposcopy; a negative case was randomized to either cytology plus HPV DNA assay one year later or immediate colposcopy.

Results: 112 women were referred to our unit during the 15-month study period (December 2016 - March 2018). One was excluded for having previous cervical treatments. The mean age was 40,7 years with 18 being post-menopausal. 64 women tested positive for p16/Ki67 immunostaining with 11 (17,1%) presenting with high grade intraepithelial lesion (HSIL) at colposcopic biopsy. One woman abandoned the follow-up and 10 were submitted to excision of the transformation zone, of which 7 presented with HSIL at the cervical cone. From the 53 women with positive p16/Ki67 immunostaining but without HSIL, 42 returned for cytology one year later and none presented HSIL. 47 women tested negative for p16/Ki67 immunostaining and were submitted to randomization: 24 were randomized to cytology plus HPV DNA assay one year later and 23 to immediate colposcopy. Of the first group, 23 came back one year later, with one presenting with HSIL at cervical cytology and another one presenting with normal cytology but positive HPV DNA assay with proven HSIL at colposcopic biopsy. Of the second group, no women presented HSIL or major colposcopic lesions at the immediate evaluation; 21 came back one year later for a new cytology and none of them presented with HSIL. In our sample, p16/Ki67 immunostaining presented a sensitivity of 84,6%, a specificity of 45,9%, a positive predictive value of 17,2% and a negative predictive value of 95,7%.

Conclusions: In our sample, p16/Ki67 immunostaining has a good sensitivity as a triage tool for women with LSIL, with an excellent negative predictive value. The greatest limitation of our study is the small number of cases, but even so we were able to show that our results are in line with those described in the literature and we believe that p16/Ki67 immunostaining will have its place in the near future as a way of screening women with LSIL.

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#0444

12 - Molecular markers

Prognostic value of FISH hybridization technique in cervical cancer patients

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Background/Objectives: Cervical cancer is one of the most common malignancies of female genital tract worldwide. The main prognostic factor of cervical cancer is represented by the disease stage together with the lymph node status. There are no available molecular markers that would have significant effect on patient survival. In our study we focused on the analysis of amplification patterns of 3q26 and 5p15 chromosomal regions and their prognostic value in 5-year follow-up.

Methods: We included 35 patients with cervical cancer, who underwent the surgical treatment in our clinic between years 2010-2014 with the follow-up of 5 years minimum. We collected liquid-based cytological samples, which underwent further analysis by fluorescent in-situ hybridization and evaluation of the amplification of chromosomal regions 3q26 and 5p15. The dependence of patients' survival on the selected predictors compared to stage and grade was modelled by the Cox proportional hazards (Cox PH) regression. In order to make an independent validation of the findings of Cox PH, we have analyzed the data also by the Survival Random Forest (SRF) machine learning algorithm.

Results: The hazards of disease relapse and consequent death during the follow-up was 5.9 (with the 95% confidence interval (1.69, 20.62)), and 1.33 (with the 95% confidence interval (1.02, 1.74)), for 5p15 and 3q26 respectively. This implies that a unit increase of 5p15 is associated with almost six-fold increase of the hazard, on average. Similarly, a unit increase in 3q26.4 is associated with a 33% average increase of the hazard.

Conclusions: Both molecular markers showed significant values regarding disease free survival and appear to be a good prognostic markers. Although we present a small study based on 35 patients, the results are promising for the next research in this field.

#0499

12 - Molecular markers

Episomal HPV16 and aggressive metastatic anal squamous cell carcinoma: molecular description by HPV Capture technology coupled with next generation sequencing; a case report.

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Background/Objectives: Herein we report the case of a very aggressive metastatic anal cancer diagnosed in an HIV infected patient who has sex with men (MSM). The metastasis was diagnosed 18 months after the initial diagnosis and resection of an HPV16-induced high-grade anal intraepithelial neoplasm (HGAIN). We have already reported the interest of using ultrasensitive droplet-based digital PCR (1) for early detection and monitoring of HPV16 circulating tumoral DNA (HPV16 ctDNA) in this patient during the metastasis genesis (1). This patient presenting a very atypical and aggressive metastatic anal cancer, we sought to study the molecular status of the HPV16 detected in the collected samples from different origins, including the initial biopsy of HGAIN, the vertebral metastasis biopsy and the plasmatic HPV16 ctDNA, using the innovative and recently described HPV Capture technology (Capt-HPV) and NGS (2).

Methods: Capt-HPV coupled with NGS is based on a generic and comprehensive HPV genome capture (208 variants from 88 genotypes) followed by NGS. (2) DNA extracts from biopsies or plasma samples have been performed manually using Qiaamp Minelute Virus Spin Kit (QIAGEN®). Sequencing was performed with an Illumina Miseq instrument. Data were automatically analyzed using a specific pipeline developed by the EGPH biomedical informatics team. HPV genotyping, HPV full length sequence, HPV molecular status (episomal or integrated), and positions of HPV/human junctions were obtained.

Results: The same HPV16 genotypes and variants (HPV16 114K) were found in the initial lesion, the plasma and the metastasis. Surprisingly, the virus appeared to be episomal in all the samples, without any integration sites in the human genome.

Conclusions: From our knowledge, this is the first longitudinal description of an HPV16 variant molecular status from HGAIN to anal metastasis conducted using the Capt-HPV technology. Interestingly, the identified molecular status of the described HPV16 variant was strictly episomal and we could not find any sign of HPV integration in the host genome while we could have expected a more atypical molecular signature regarding the particular physiopathology of this very aggressive metastatic anal cancer. This result could have further implications for treatment management and follow-up.

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#0603

12 - Molecular markers

IMMUNOHISTOCHEMISTRY MARKERS IN THE DIAGNOSIS OF H-SIL

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Background/Objectives: Cervical cancer is a widespread disease worldwide, with an annual incidence of 13.2 per 100,000 women and an annual mortality rate of 5.9 per 100,000 women per year. Cervical diseases preceding invasive cervical cancer include epithelial dysplasia or cervical intraepithelial neoplasia (CIN). The concept of carcinogenesis implies a consistent progression from CIN 1 to CIN 2 and CIN 3, cancer in situ (CIS) and the development of invasive cancer against the background of persistent HPV infection of high carcinogenic risk. Objective: to evaluate immunohistochemical profiles of different stages of dysplastic transformation of the cervix

Methods: immunohistochemical study (IHC) to evaluate the expression of markers P16 INK4a, Cyclin D1, Ki-67 Material: 56 deparaffinizing slices from tissue blocks of uterine cervix obtained from loop electrocautery excision (conization) area of transformation. 31 samples of cervical tissue of patients with HPV infection but without CIN, CIS were used as control

Results: was obtained the following expression levels of biomarkers for CIN1: ki-67 in surface epithelium 11-20% in glands 7-13%, P16 INK4a in the surface epithelium of 4-8%, Cyclin D1 in surface epithelium and glands 10-11%; CIN 2 for ki-67 in surface epithelium 55-75%, in the glands 73-91% P16 INK4a in the surface epithelium of 50-60%, in the glands 80-95%, Cyclin D1 in surface epithelium and glands 8-9%; for CIN 3 ki-67 in surface epithelium 85-95%, in the glands 92-95%, P16 INK4a in the surface epithelium of 70-80%, in the glands 96-98%, Cyclin D1 in surface epithelium and glands 5-6%; for CIS ki-67 in epithelium 96-100%, in glands 96-100%, P16 INK4a in epithelium 96-100%, in glands 96-100%, Cyclin D1 in epithelium and glands 3-4%

Conclusions: immunohistochemical study with the determination of the expression of markers P16 INK4a, Cyclin D1, Ki-67 in dysplastic cells provides prognostic signs of cell proliferation with an unfavorable prognosis at the stage of early cell changes, when colposcopy, cytological and histological examination is not effective enough to clarify the diagnosis of cervical dysplasia

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#0053

13 - Screening for women difficult to reach

Implementation of primary and secondary cervical cancer prevention in the Regional center of cervical pathology

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Background/Objectives: To analyse the application of the methods of cervical cancer (CC) prevention in the Regional center cervical pathology (RCCP) Rostov-on-don.

Methods: In 2008, the RCCP was organized on the basis of the clinical and laboratory complex of the Regional consultative diagnostic center (OCD) in Rostov-on-don, where the office of human papillomavirus (HPV) vaccination began its work. In 2012 the program of CC screening with the method of liquid-based cytology was introduced for the first time in Russia. It covered 54 medical organizations of the Rostov region (RR). HPV positive patients with abnormal PAP smears are invited to RCCP for making a diagnosis and treatment.

Results: During 2008 - 2018 released 23 newsletters and the booklet were put out, 5 round tables were held for the female population of RO on the etiology and treatment of cervical cancer, the possibilities of vaccination in RCCP. 73 and 86 women aged 18 to 45 years were vaccinated with a twovalent and quadrivalent vaccines respectively. From 2014 to 2017, 188 641 cytological studies were performed, CC being revealed in 189 women - 0.1 % , H-SIL and ASCH in 566 (0.3 %), ASCUS in 377 (0.2%), L-SIL in 23014 (12.2%), absence of intracellular lesion or malignancy (NILM) in 164495 (87.2%). 2162 HPV - positive women aged 19 to 69 years were invited to see a gynecologist in the RCCP. Treatment with conization (622) and cervical excision (830) was performed in 1452 patients. H-SIL and CIS in 1162 women (78%).

Conclusions: Primary prevention of cervical cancer is implemented mainly by means of informing the population, the introduction of HPV vaccination is significantly limited by the lack of a state program. Regional screening program with an active call of patients, using such diagnostic method as liquid base cytology and HPV testing, allow timely detection and treatment of precancerous lesions of the cervix, i.e. to carry out secondary prevention of cervical cancer.

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#0437

13 - Screening for women difficult to reach

Prevalence of CIN2+ among ASCUS smears in Isère department

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Background/Objectives: The objectives of the study is to investigate the evolution of the ASCUS rates among the smears performed in the cytology laboratories involved in the Isere cervix cancer screening programme.

Methods: The screening centre registrate all the smears made by women aged 25 to 65 and living within the local area of Isere. The smears results are transmitted by the pathologists using a data extraction. The reporting system for the cytology results is Bethesda, with an initial classification using the French ADICAP codification. The screening center, as a part of the quality assurance of the programme, gives the pathologists units their positives rates each year. These data include the rates for ASCUS smears and the other sub types of positives. The Ascus smears rates have been calculated every year and monitored. The strong progression of this rate in some pathologists units lead us to investigate the problem and explore the prevalence of CIN2+ lesions in these pap tests.

Results: During the first three years of the monitoring (2011-2013), 351 ASCUS (1.03%) were found among 34234 satisfying smears performed. Most of these women were followed by repeated cytology and only 54 had a biopsy (15.4%), from immediate colposcopy or following a positive control smear. Among the ASCUS smears, 3,7% of women were detected having CIN2+. During the subsequent years (2014-2016), 1777 ASCUS were identified among 49416 satisfying tests, processed in the same pathologist units, ie 3.6%, resulting in a 3 fold initial rate. In the ASCUS population, CIN2+ was detected in 5,3% women, with a similar proportion of women followed with colposcopy and biopsy.

Conclusions: In a screening programme, the observation of a sharp progression in ASCUS rates in some pathologist units, must be analysed in correlation with the CIN2+ prevalence. An internal reorganisation including liquid based cytology, training of cyto-technicians and quality control process can lead to this progression, corresponding to an increase in detection of pre-cancerous pathology.

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#0517

13 - Screening for women difficult to reach

Organized vs. Opportunistic Screening: A Portuguese Oncology Centre Experience

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Background/Objectives: The implementation of organized screening programs for cervical cancer allow early detection of the disease. Abnormalities found on screening require follow-up, diagnosis and treatment, in order to prevent the development of cancer or to treat cancer at an early stage. We are involved in the national organized screening program for cervical carcinoma prevention. Prior to this screening our hospital participated with Santa Casa da Misericórdia in an opportunistic screening program for women with difficulties in accessing primary healthcare. To compare the results of these two types of screening: opportunistic screening and organized screening.

Methods: A total of 2366 women were screened with HPV HR test, 1789 were screened in the national screening program and 577 were screened opportunistically. All HPV16 or HPV18 positive women were referred for colposcopy. Other HR HPV types detected were sent for cytological screening. When abnormalities are detected on the cytology, women were referred for colposcopy.

Results: For women attended the opportunistic screening the average age was 39,2 years (range 18-71), while the mean age for women on the organized screening was 45,9 years (range 29-66). The percentage of women positive for at least one type of HRV is higher in the group of opportunistic screening (36.4% vs. 10.4%). In terms of mixed infections, they are more frequent in the organized screening (29.8% vs 24.7%). The exception was for the group of women under 30 years of age (33.3% vs 44.3%). HPV infection tends to decrease with age in organized screening, but not in opportunistic screening, where the percentage of infected women is higher and constant regardless of age. The percentage of women referred for colposcopy after HPV testing was also higher in opportunistically screened women, which was related to the high prevalence of HPV16 found in this group (47.1%). In terms of cytological results the major difference lies in the large percentage of ASC-US detected in organized screening (21.0%) compared to the percentage detected in opportunistic screening (4.8%). In terms of reactive changes and infections detected on cytology no differences were found between the two groups.

Conclusions: There are differences between results obtained for both types of screening. The high rate of HPV infection on opportunistic screening may be explained by the fact that women who have been screened opportunistically have more difficult access to healthcare. However difference in size of the two groups analyzed may also bias the results. In the organized screening, unlike to opportunistic, the cytologists were aware of the HPV test results, which could influence the results raising the number of ASC-US diagnosis.

#0212

13 - Screening for women difficult to reach

HPV prevalence and HPV-related dysplasia in elderly women

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Background/Objectives: In Sweden, about 30% of cervical cancer cases occur in women older than 60 and the mortality rate is about 70% in this age group. Cervical cancer in women above the age of 65 is usually discovered at advanced stages and the prognosis is poor. The life expectancy for Swedish women is 84 years. Many women over 65 are healthy, continue to work and have an active sex-life. The aim of this study was to investigate the prevalence of HPV and cervical dysplasia in women of 60 years and above

Methods: From September 2013 to June 2015, 1051 women aged 60-89 years (mean 68 years) were sampled for an HPV test when attending an outpatient gynecology clinic. Women with positive results had a second HPV test and liquid based cytology (LBC) after 3.5 months on average. Those with a positive second HPV test were examined by colposcopy, and biopsy and a sample for LBC were obtained.

Results: The prevalence of HPV was 4.1%, (95%CI 3.0-5.5, n = 43) at the first test, and at the second test 2.6% remained positive (95%CI 1.7-3.8, n = 27). Loss of detection of HPV between test one and two was 37.2% when the second HPV test was done on average 3.5 months after the first test. The majority of women positive in both HPV tests, had dysplasia in histology, 81.5% (22/27) (4 CIN 2±0.4%, 18 CIN 1±1.7%). The positive predictive value of CIN2+ was 14.8%. HPV-related dysplasia was found in 2.1%, (95%CI 1.3±3.2, n = 22) of the 1051 women. Four of the 22 women with positive HPV tests also had abnormal cytology, one ASCUS and three CIN 1. No cancer or glandular dysplasia was detected.

Conclusions: A significant proportion of elderly women were found to have a persistent cervical HPV infection. Among them, there was a high prevalence of CIN diagnosed by histology. The HPV test showed high sensitivity and specificity in detecting CIN in elderly women, while cytology showed extremely low sensitivity. We hope that our results will serve as motivation to conduct studies focusing on older women also, in order to effectively reduce the prevalence of cervical cancer in this age group.

17 - Methylation

DNA methylation analysis in HPV-positive screening samples from women 30-69 years in the cervical cancer-screening program in Örebro, Sweden - a pilot study

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Background/Objectives: In Sweden, new recommendations for cervical cancer screening has been in place since 2016, where women between the age of 30 and 69 years should be screened using HPV test and a hrHPV-positive result followed by a cytology evaluation. In the Örebro region, an mRNA- based test is used (Aptima, Hologic) for HPV primary screening where a positive or negative test result for 14 hrHPV is given. Cytology as a triage method after a HPV positive test is widely accepted and used. Other triage methods have been discussed and DNA hypermethylation analysis in certain host cell genes is one. DNA hypermethylation is suggested to be a promising molecular triage method comparable to cytology and could unlike cytology be implemented in a program with self-collected cytology sampling. The aim was to evaluate the DNA methylation state of the HPV-positive samples in the cervical cancer screening cohort and its association to the cytology- and HPV-status.

Methods: mRNA HPV screening- positive samples (Aptima, Hologic) between November 2016 and April 2017 were collected (n=529), and 27 of these were analyzed in the current pilot-study. The samples have been genotyped with Anyplex II HPV28 (Seegene), detecting 28 different HPV genotypes. Two commercially available kits were used to analyze hypermethylation of host cell genes. The first method, QIASure (Qiagen), evaluates methylation status of two human target genes (FAM19A4 and mir-124-2) and one control gene (ACTB). Detected hypermethylation in any of the targets results in a positive test result. The second method, GynTect (Oncnostics), analyzes six human target genes (ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671) and two control genes (ACHE and IDS-M) and gives a methylation score which sums up to a positive or negative result for the sample.

Results: With QIASure 9 of the 27 samples were positive for hypermethylation, 2 samples were invalid and 16 were negative. From analysis with GynTect 9 out of 27 samples showed positive and 18 negative results. The result concordance between the two methods was 76 % and the sensitivity of detecting cytological HSIL/CIN2+ was 63% for QIASure and 67 % for GynTect in this pilot study. There was no statistically significant difference of hypermethylation positivity between groups of samples containing single vs. multiple number of HPV genotypes (Fishers exact test; p=0.229).

Conclusions: The two methods evaluated to detect hypermethylation in biobanked cervical cell samples both gave valid results and were comparable in this small pilot study. Further analysis with larger sample size is ongoing.

#0391

17 - Methylation

The methylated PAX1 gene used as follow up biomarker for cervical intraepithelial neoplasia and cervical cancer treatment

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Background/Objectives: To evaluate the efficacy of methylated PAX1 gene (PAX1m) as follow up biomarker for clinical intraepithelial neoplasia and cervical cancer treatment (conization or surgery) strategy.

Methods: The subjects were recruited in Fujian Provincial Cancer Hospital in China from January, 2018 to July, 2019. The inclusion criteria were the positive result of PAX1m test before surgery or conization patients with cervical cancer or cervical intraepithelial neoplasia. The exclusion criteria were negative result of PAX1m test before treatment for cervical cancer or cervical intraepithelial neoplasia. The result of PAX1m test was performed and determined by using Hoomya methylation Q-PCR system. The high-risk HPV test was determined by cobas 4800 system, Roche. The cytology results were performed by Thinprep cytology system. All the three tests (cytology, HPV-HR, and PAX1m) were tested every 3-6 months after treatment. One of the positive results of the three tests after treatment was performed by histology after colposcopy.

Results: Eighty-three PAX1m positive of total 204 patients before treatment were recruited and analyzed in the study. The patients were 135 of CIN1 for observation, 48 of CIN1/2/3 for conization, and 21 of carcinoma in situ/ squamous cell carcinoma for hysterectomy. More than 95% of the after-treatment patients in the study were PAX1m negative results at the first-time follow up observation. All the 21 patients with hysterectomy were all negative PAX1m results after one year follow up with no recurrence by standard gynecological check. Twenty-one of 48 conization patients were HPV16 or high risk HPV positive results after 6 months follow-up and 4 of them were positive results of PAX1m test after 12 months. Three of the positive results of PAX1m patients were over CIN1 results by histology-colposcopy after 18 months. Four of the 135 CIN1 observation patients, over 86% high risk HPV, were all detected positive results of PAX1m with progression by gynecological check.

Conclusions: The current results indicated that the real time PCR-based testing for PAX1m is promising and better follow up biomarker than high risk HPV genotyping or cytology tests for cervical neoplasia and cervical cancer treatment patients.

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#0226

18 - Microbiome

CERVICAL MICROBIOTA IN WOMEN WITH CERVICAL INTRA-EPITHELIAL NEOPLASIA, PRIOR TO AND AFTER LOCAL EXCISIONAL TREATMENT, A NORWEGIAN COHORT STUDY.

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Background/Objectives: Local treatment for cervical intraepithelial neoplasia (CIN) by Loop Electrosurgical Excision Procedure (LEEP) has been correlated with reproductive morbidity, while the cervicovaginal microbiota is also known to affect the risk of preterm delivery. CIN and treatment by LEEP might change the cervical microbiota. The main aim of this study was to describe the cervical microbiota before and after LEEP and assess its association with cone depth and HPV persistence. Further, we aimed to compare the microbiota to references with normal cervical cytology.

Methods: Between 2005 and 2007, we prospectively identified 89 women planned for LEEP in a Norwegian hospital and recruited 100 references with a normal cervical cytology. Endocervical swabs were collected prior to treatment and at six (n = 77) and 12 months (n = 72) post LEEP for bacterial culture and PCR, and post LEEP for DNA testing for human papillomavirus (HPV). We compared the cervical microbiota composition before and after treatment and between women planned for LEEP vs references.

Results: There was a reduction in the number of non-Lactobacillus bacterial species six and 12 months after LEEP compared to before treatment and a tendency towards a concomitant increase in Lactobacillus. No association between the detection of cervical bacteria, HPV persistence or cone depth was found. Women planned for LEEP carried significantly more Bacteroides spp., Gardnerella vaginalis, Mycoplasma hominis and Ureaplasma parvum as well as a greater number of bacterial species than the references.

Conclusions: Local excisional treatment appears to alter the cervical microbiota towards a less diverse microbiota. Women with CIN have a more diverse cervical microbiota compared to women with normal cervical cytology.

RELATIONSHIP BETWEEN VAGINAL MICROBIOTA AND HPV INFECTION

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Background/Objectives: Objective: 1) To evaluate the vaginal dysfunction through the basic vaginal states (BVS) by the Vaginal Content Balance (BAVACO) methodology and the presence of lactobacillar microbiota in patients with low-grade and high-grade HPV related lesions (LSIL and HSIL respectively) in comparison with control group. 2) To characterize the Lactobacillus species associated with these lesions.

Methods: Consecutive, prospective, descriptive and cross-sectional study. We examined 760 patients between 18 and 50 years old with onset of sexual intercourse. All patients underwent clinical examination and a sample from vaginal fornix was taken to study BVS by BAVACO and culture. The identification of lactobacilli species was performed by mass spectrometry (MALDI-TOF). The Chi square and Fisher test were used to compare the vaginal dysfunction and the lactobacillar microbiota of the study population with the control. A $p < 0.05$ was considered significant.

Results: We analyzed 760 patients, which were divided in two age groups: Group 1: 18-24 years old ($n = 175$) and Group 2: 25-50 years old ($n = 585$). Both groups were subdivided into LSIL and HSIL according to their lesions. The prevalence of BVS of unbalance vaginal content (III, IV and V) was for the Group 1: control subgroup 37.9% (50/132), LSIL subgroup 56.7% (17/30 / $p = 0.047$) and HSIL subgroup 66.7% (8/12 / $p = 0.05$). For the Group 2 the prevalence of BVS of unbalance was as follows: control subgroup 39.4% (196/498), LSIL subgroup 50.0% (23/46 / $p = 0.21$) y HSIL subgroup 48.6% (18/37 / $p = 0.17$). The most prevalent pathogen was bacterial vaginosis (BV) in both groups ($p < 0.001$). The prevalence of BV in Group 1 was as follows: Control 35.6%; LSIL 46.7%, HSIL 58.3%, while in the Group 2, Control 32.5%; LSIL 47.8%, HSIL 43.2%. As regards the Lactobacillus species, patients with HSIL had a prevalence of 21.4% of *L. crispatus* and 46.2% of *L. jensenii*.

Conclusions: A greater unbalance of the vaginal microbiota was observed in LSIL and HSIL subgroup patients than in Control subgroup in both age groups studied; especially in the HSIL subgroup, in which a low prevalence of *L. crispatus* (protective species) and an increase of *L. jensenii*, a species that has a lower protective role of vaginal dysfunction, was found. Therefore, it is important to characterize Lactobacillus species, since the increase in non-protective species in coincidence with the increase in BV in this group of patients, alters the vaginal microenvironment and may act as potential cofactors in the persistence of HPV infection, also increasing the risk of acquiring other sexually transmitted infections.

#0068

20 - New technologies

THE CAUSES FOR DUAL P16/KI-67 EVALUATION FALSE RESULTS ON CONVENTIONAL SMEARS

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Background/Objectives: After the training program for the evaluation of dual p16/Ki-67 immunocytochemical staining (ICS) on conventional smears two students had a high rate of false results (positive and negative) according to CIN2+. We aimed to identify the causes behind the false results.

Methods: Two students (S), a biologist (S1) and a medical doctor (S2) with no prior knowledge in gynecological cytology and ICS, participated in the previously described training program for p16/Ki-67 ICS reading (1). After the training S evaluated 383 p16/Ki-67 ICS slides of women from a colposcopy clinic, where a biopsy was performed in case of an abnormal colposcopy. All slides were reevaluated by a senior cytotechnologist (SC) and slides with discordant results by a consensus of 5 pathologists and 3 cytotechnologists (reference). Percentages of cases where dual p16/Ki-67 stained cells were overlooked, misinterpreted or absent were determined for each evaluator. The p16/Ki-67 positive cells were overlooked when the positive cells were on the slides, but the evaluator didn't see them. The result of p16/Ki-67 staining was misinterpreted when the evaluator interpreted positive cells as negative and negative cells as positive.

Results: The false positive and negative rates for S1, S2, SC (S1), SC (S2) and reference were 28.9%, 17.0%, 21.7%, 22.2%, 16.4%, and 2.6%, 3.1%, 3.1%, 3.4%, 2.1%, respectively. The SC results were similar to the S1 results and not as good as reference results. In 8/383 slides dual p16/Ki-67 stained cells were absent. S1, S1, SC (S1), SC (S2) and reference misinterpreted dual p16/Ki-67 stained cells in 111 (29.0%), 65 (17.0%), 83 (21.7%), 85 (22.2%) and 63 (16.4%) slides. On the other hand, they overlooked few dual p16/Ki-67 stained cells: 4 (1.0%), 7 (1.8%), 5 (1.3%), 5 (1.3%) and 0 (0%).

Conclusions: There were less false negative than false positive results; most of the false negatives were due to overlooked dual-stained cells. The main cause for false positive results was misinterpretation of p16/Ki-67 stained cells.

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#0207

20 - New technologies

AN INFECTIOUS PSEUDOVIRION OF HPV WITH THYMIDINE KINASE AS A TOOL OF GENE THERAPY

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Background/Objectives: Human papillomavirus (HPV) infection causes an estimated 5% of total human cancers. Among 18 high-risk types of HPVs, especially HPV16 and HPV18, act as an etiologic agent of HPV-associated cancers. Because the HPV life cycle depends on the host cell differentiation program, native HPV virions are produced only in vivo or in organotypic culture. Therefore, synthetic HPV particles such as virus-like particles (VLPs) and infectious pseudovirions (PsV) have been substituted for native HPV virions to study HPV biology. The further ability of HPV-PsV to deliver DNA into cells suggests several potential applications including DNA vaccines and gene therapies. In the present study, we have developed a new PsV harboring a plasmid containing herpes simplex virus thymidine kinase (HSV-TK) sequence to confer sensitivity to the nucleoside analogs such as ganciclovir to the infected cells as a tool of gene therapy.

Methods: To generate PsV harboring TK encoding plasmid, we constructed codon-optimized HPV16 capsid genes, L1 and L2. Bovine papillomavirus requires E1 DNA sequence to encapsulate a reporter plasmid (Zhao et al., 1999). But it has not yet elucidated what sequence should be needed to efficiently package into HPV-VLPs. To identify the sites required for packaging, E1 was divided into several parts and inserted reporter plasmids, and each of which was used to produce PsV in modified several methods reported (Buck et al., 2004, 2005, 2007). And we performed infectivity assay which successful encapsulation of the plasmid contained GFP was functionally evaluated by quantifying infection of 293FT cells, as determined by the percentage of green fluorescent cells using flow cytometry.

Results: The result was that DNA can be packaged to produce an infectious PsV using a reporter plasmid containing either region of E1. Next, because this HPV-PsV contains HsV-TK, when the HSV-TK gene is expressed, it acts on ganciclovir and turns it into a toxic substance with DNA synthesis inhibitory activity and has a suicide function that leads to death by apoptosis. We inoculated several cells with PsV and administered ganciclovir. The result was that the number of survived cells after ganciclovir treatment was significantly less than that of cells not exposed to ganciclovir.

Conclusions: We developed the new infectious HPV-PsV that can lead to cell death with ganciclovir when infected. We believe the potential for new gene therapies will expand by adapting this PsV to cancer cells.

#0210

22 - Diagnostic procedures / management

TOWARDS IDENTIFICATION OF HPV DIAGNOSTIC AND PROGNOSTIC BIOMARKERS USING MACHINE LEARNING ON HPV INTEGRATION CLINICAL DATA OBTAINED BY MOLECULAR COMBING.

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Background/Objectives: Background: Integration of High Risk-HPV (HR-HPV) DNA into the host genome is a major step in the progression of cervical neoplasia. Molecular combing associated with a Genomic Morse Code (GMC) is a powerful technology to visualize and monitor chromosome rearrangement and was successfully used to detect and quantify HPV integrated sequences into the host DNA. Objectives: The EXPL-HPV-002 clinical study is currently conducted in Czech Republic on 410 HR-HPV positive patients to evaluate whether the virus integration is a biomarker of the severity and the progression of cervical lesions. A first statistical analysis process gave promising results, so we decided to complete data mining with a machine learning approach. The objective is to refine the biomarkers and develop a diagnostic and prognostic test that would help the clinician to adjust patient care.

Methods: Methods : Many data including cytology, colposcopy, HPV genotyping and histology status are collected at inclusion visit and after 6, 12, 18, 24, 30 and 36 months of follow-up. Molecular combing analyses are performed on cervical sampling at T0, 12, 24 and 36 months. The informations entered in the study database were used to perform a machine learning method using multiple variables for the classification of patients' histologies. An over-sampling method (SMOTE) was used to increase the data quality and « Gradient Boosting Decision Tree » algorithm (XGBoost) was applied - a supervised machine learning algorithm that creates «learners» (decision trees) and combines them into one strong learner. To select the most critical variables, we used « Shapley » values, a solution concept in cooperative game theory, which works by adding/removing a specific variable and compares the prediction success in the presence/absence of it. Then we chose the most relevant statistical model showing the best diagnostic and prognostic performances.

Results: Results : Combining clinical and virus integration variables, we were able to identify promising predictors able to reveal the severity and the potential evolution of cervical lesions after HR-HPV infection.

Conclusions: Conclusion: Although the longitudinal phase of our study is still ongoing, we can already conclude that machine learning approach allowed us to identify powerful signatures combining clinical and HPV molecular combing datas able to work as strong diagnostic and prognostic predictors of patient histology state.

#0488

22 - Diagnostic procedures / management

Adenosarcoma in cervical polyp

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Background/Objectives: Uterine adenosarcoma is a rare tumor. It accounts for 5% of all uterine sarcomas. Adenosarcoma belongs to the group of mixed mesenchymal tumors originating in the endometrium. They consist of a benign glandular epithelium and a sarcomatous stroma. Factors that affect prognosis include sarcomatous overgrowth, lymphovascular invasion, invasion of the uterus, the presence of necrosis and heterologous elements. Most patients seek medical attention at 1 stage of the disease, where the 5-year survival is 60 to 80%. Due to the rarity of the tumor, there is little data describing the optimal therapeutic treatment. Hysterectomy with bilateral salpingo-oophorectomy is the method of choice. There are no explicit recommendations for adjuvant chemotherapy or radiotherapy. However, some researchers indicate the prognosis might improve in patients with sarcomatous overgrowth after the inclusion of adjuvant chemotherapy or hormone therapy in some types of tumor.

Methods: 43-year-old female patient was referred by the physician due to cervical polyp. After being admitted to the hospital, the patient was qualified to remove the polyp and perform cervical curettage. The material was sent for histopathological examination. Low grade adenosarcoma was obtained from the polyp removed from the cervix - CD 10 (+) SMA (+/-) Ki 67 2% stromal immunoassay.

Results: Due to the fact that the histopathologist was not able to determine if the lesion was removed radically, the patient was qualified for a radically modified hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy. In the final histopathological result, no tumor changes were found.

Conclusions: Final histopathological diagnosis presented cervical adenosarcoma low-grade pT1a, pN0. Chemotherapy was discontinued. Further oncological supervision over the patient was recommended.

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#0073

23 - Colposcopy

DOES DYNAMIC SPECTRAL IMAGING COLPOSCOPY IMPROVE THE DIAGNOSTIC ACCURACY OF CERVICAL DYSPLASIA?

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Background/Objectives: New adjunctive colposcopy technologies are available to assist with colposcopy by providing a more objective approach. It has been suggested that Dynamic Spectral Imaging (DSI) colposcopy improves sensitivity and diagnostic accuracy of the colposcopy exam. However, none of the previous studies have compared the diagnosis of the cervical biopsies with the final excisional procedure diagnosis. The purpose of our study was therefore to examine how well the diagnosis of the different biopsies taken from the cervix, agree with the final excisional procedure diagnosis, and evaluate if DSI colposcopy will improve the diagnostics of treatment demanding cervical dysplasia.

Methods: In a prospective clinical study 573 women were included at the Regional Hospital in Randers, Denmark. All women were examined with a DSI colposcope and 4 biopsies were taken from the cervix according to the national guidelines by the Danish Society of Obstetrics and Gynaecology. Colposcopy was performed by trained nurses, residents and consultants. The first biopsy taken was the colposcopic directed biopsy and marked by the colposcopist before the DSI map was revealed. The second biopsy was marked from the worst area indicated by the DSI map. Two further, random, biopsies were taken. If any of the 4 biopsies indicated cervical dysplasia of such a degree that an excisional procedure was indicated the patient was referred for a loop electrosurgical excision procedure (LEEP). In total 170 women underwent LEEP, 124 of these women had fully or partially visible transformation zones (TZ) of the cervix during colposcopy. The diagnoses of the biopsies were compared to the LEEP diagnosis.

Results: The colposcopic directed biopsy agreed with the worst area indicated by the DSI map in 62.9% of the cases. We found that the DSI directed biopsy (83.9%) had a relative increase of 4.1% in perfect agreement with the LEEP diagnosis than the colposcopic directed biopsy (80.6%). Considering all 4 biopsies; there was perfect agreement in 95.2% cases.

Conclusions: By comparing biopsy diagnoses to LEEP diagnosis we did not find, an increased performance of the DSI colposcope of the same magnitude as previous studies. We found the DSI technology and the colposcopic directed biopsy to be equal. The DSI technology can therefore be used to assist in choosing the worst area to biopsy and may provide support to less experienced colposcopists.

EFFECTS OF ORALLY ADMINISTERED PRELIMINARY ANALGESIC THERAPY IN DIAGNOSTIC COLPOSCOPY PATIENTS: A PROSPECTIVE QUESTIONNAIRE STUDY

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Background/Objectives: Despite the abundance of valid information on HPV infection, most women who undergo colposcopy experience varying degrees of stress/anxiety and sometimes pain. Based on a University Hospital Colposcopy Clinic in Northwestern Greece, we conducted a single-center prospective study with the primary aim to investigate the efficacy of preliminary administration of paracetamol in terms of pain and anxiety relief, when given per os, 30-60 minutes before a diagnostic colposcopy procedure.

Methods: We recruited women who were about to undergo diagnostic colposcopy, either as a first, or as a repeat procedure. Permission was granted from the University Hospital's Scientific - Ethics Committee before patient enrollment commenced. Our study population consisted of 112 patients with suspected or confirmed cervical pathology. HPV-Vaccination status was not recorded. Procedures were strictly diagnostic, when biopsies were considered as part of the management; they were arranged for a later appointment. Following the exam, colposcopic findings, management options and an overview of the treatment plan were discussed with the patient. At the end of consultation, each patient completed a special anonymous questionnaire which has been specially developed for the purposes of the study and then returned it to the attending midwife. Statistical analyses were performed implementing IBM SPSS v24 statistical package.

Results: In the control group, most patients considered the pain as nil to moderate, only 3 women considered the experienced pain as severe. In contrast, in the paracetamol group, all patients experienced nil to moderate pain. No patients in the paracetamol group rated the pain as severe. Similarly, anxiety levels were comparable among both groups. Almost 90% of women in both groups experienced nil to moderate levels of anxiety and only the remainder 10% experienced moderate to severe anxiety.

Conclusions: Several interventions to reduce colposcopy-related pain and anxiety, mainly implementing music can be found in the literature, but this is the first study to examine the efficacy of P.O. paracetamol in this setting. Despite the marginal results in our study, preliminary medication could have a beneficial role in patients undergoing diagnostic colposcopy. The level of knowledge patients have regarding colposcopy itself might influence anxiety and pain levels during the procedure.

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#0054

24 - Cervical neoplasia

Management of cervical intraepithelial neoplasia 2 in young women

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Background/Objectives: Current treatment guidelines indicate that when cervical intraepithelial neoplasia (CIN) 2 is specified on biopsy in women younger than 24, observation is preferred. The purpose of this study is to evaluate the effectiveness of conservative management of CIN2 in Korean young women and to find appropriate management strategy considering age.

Methods: A total of 129 women ≤ 30 years who were diagnosed with CIN2 on punch biopsy was retrospectively reviewed. Patient characteristics and initial and follow-up results of cervical examinations including pap smear, human papillomavirus (HPV), and punch biopsy were collected. Treatment was categorized into three: observation (n=30, 23.3%), ablation (n=15, 11.6%), and excision (n=84, 65.1%). Recurrence was counted when high-grade lesions on pap smear or CIN1+ in biopsy were detected. Recurrence and recurrence-free survival (RFS) were compared between treatment categories. Survival analysis with Cox proportional hazards regression model was used.

Results: Median age was 27 years (range, 14-30). Patients in excision group were older than the other groups (median, 28 vs. 26 years; $p < 0.001$). Median follow-up was 16 months (range, 0-132 months). There were 14 recurrences (10.9%): 8 CIN1 and 6 CIN2. Patients who were followed up with observation had more frequent recurrences (recurrence rate, 23.3% vs. 7.1%; $p = 0.019$) than those who were treated with ablation or excision (treatment group) despite lower rate of HPV-16, 18(+) (10.0% vs. 30.3%; $p = 0.026$). There was no difference in recurrence rate between ablation and excision throughout all age groups (6.7% vs. 7.1%). Observation (HR, 7.2; 95% CI, 2.0-26.0; $p = 0.003$) and HPV 16, 18 (+) (HR, 4.4; 95% CI, 1.3-15.0; $p = 0.018$) were independent factors for early recurrence. Age was not an independent factor. In patients ≤ 24 years, however, HPV 16, 18 (+) was the only independent factors for early recurrence (HR, 23.3; 95% CI, 1.9-285.3; $p = 0.014$). In subgroup analyses of the other age criteria, observation remained as an independent factor.

Conclusions: Observation without any treatment appears to increase early recurrence in women ≤ 30 years with CIN2. Ablation or careful follow-up could be appropriate management particularly in young women ≤ 24 years, which is consistent with the current guidelines of western countries.

#0572

24 - Cervical neoplasia

HPV16-associated adenocarcinoma

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Background/Objectives: Introduction: Cervical cancer is the 4th most common female cancer, despite the implementation of screening programs and the development of vaccines against human papillomavirus - HPV. Cervical cancer is still regarded today as a public health problem. Risk factors are given greater emphasis to persistent infection by high-risk HPV subtypes, particularly 16 and 18. Adenocarcinoma has been increasing, especially in young women and in developed countries.

Methods: Clinical case: Woman 44A referred to colposcopy unit for ASC-US +HPV 16 Menarche -11A, Coital - 23A, Partners - 2, G2P2 HCC since 22A, non-vaccinated and non-smoking Adequate colposcopy, ZT 2, extensive immature metaplasia At 6 months - colposcopy - adequate, ZT 2, grade 2 colposcopic findings.

Results: DH Biopsy - in situ adenocarcinoma focus - Excision of transformation zone - HD -adenocarcinoma in situ margins without dysplasia - Total hysterectomy + bilateral DH salpingectomy - cervix without significant changes At follow up at 6 months NILM cytology

Conclusions: Cervical cytology has a low sensitivity, because unlike the squamous cells, the endocervical cells are particularly cohesive with limited smear collection. The diagnosis is complicated by the difficult cytopathological differentiation between glandular atypia and benign changes such as metaplasia. In situ adenocarcinoma is the only lesion established as a precursor to invasive cervical adenocarcinoma. Treatment and monitoring of lesions in situ or in early stages of invasion is sometimes controversial and challenging.

References:

#0281

24 - Cervical neoplasia

EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN A HIGH-RISK HPV INFECTED PATIENTS. RESULTS OF DIFFERENT STUDIES.

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Background/Objectives: New and independent real-life data about the high-risk HPV (HR-HPV) clearance effect of a non-hormonal Coriolus versicolor-based vaginal gel (CVVG) have been presented in the last years. The objective of this work was to evaluate the consistency of the HPV clearance effect of this gel in patients infected by HR-HPV across these studies and a clinical trial.

Methods: Results from 3 independent observational non-comparative studies carried out in 3 different public centers of Spain were evaluated and compared to results from a randomized, open, parallel and controlled clinical trial comparing the CVVG vs wait and see approach (The Paloma RCT). One of the independent studies was prospective (Vigo study)¹ and the two others were retrospective (Coruña and Hospitalet studies)^{2,3}. Vigo study¹: HPV clearance at 6 months of 25 patients older than 24 years infected by HPV 16 and/or 18 was evaluated as a secondary endpoint. Coruña study²: 57 medical records of patients with HR-HPV (mean age 38.4 years) were analyzed. HPV clearance at 6 months was evaluated as primary endpoint. Hospitalet study³: Data of 91 HR-HPV patients aged between 20 and 65 were evaluated. Primary endpoint: composite efficacy variable (percentage of patients with normal cytology and/or HPV clearance at 6 months). Paloma RCT: 66 HR-HPV patients (mean age 39,73 years) were evaluated (41 vs 25 in CVVG and control groups, respectively). Percentage of patients with HR-HPV clearance (total clearance + partial clearance with concordant cytological and colposcopy normalization) at 6 months was assessed as secondary endpoint.

Results: After the 6 month treatment period, 48% of patients cleared HPV 16-18 (Vigo study), a reduction of 58% was observed in number of HR-HPV patients (Coruña study) and 72.5% of patients negativized cytology and/or cleared HR-HPV (Hospitalet study) vs baseline ($p \leq 0.0001$ for all results, Chi-square). In the Paloma RCT, HR-HPV clearance was observed in 63% of patients treated with CVVG vs 40% in the control group ($p=0.076$).

Conclusions: After the 6 month treatment period, CVVG has shown significant and consistent rates of HR-HPV clearance ranging from 50% to 70% in the 4 different studies carried out. Data of further studies should confirm these exciting results.

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#0072

24 - Cervical neoplasia

CASE REPORT OF AN ALTERNATIVE TREATMENT FOR RECURRENT CERVICAL AND VAGINAL DYSPLASIA IN PATIENT WITH PERSISTENT HPV INFECTION

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Background/Objectives: The standard therapy for genital intraepithelial neoplasia is surgical. However, this modality of treatment does not treat the etiological factor - HPV. Objectives: To evaluate the clinical response to imiquimod 5% cream for recurrent CIN and VAIN in patient with persistent HPV infection.

Methods: A 29 years old woman complained for giant condylomas in vulvar and perineal areas. HPV test positive (6, 16 types), cervical cytology PAP HSIL. Colposcopic images before treatment on picture 1 and 2. The patient was nulliparous, did not smoke, nor used hormonal contraceptives or had immunosuppressive diseases. Surgical excision of condylomas and cervical conization were performed. The histological finding was CIN 2. The patient got pregnant and delivered a healthy baby in 2 years and continued follow-up by gynecologist. During next 2 years persisted cervical dysplasia CIN 2, positive HPV test 6, 16, 31, 52 and vaginal neoplasia appeared with histological finding VAIN2. The use of vaginal and cervical imiquimod 5% cream was undertaken to treat the patient. 250 mg of cream was placed in the entire cervix and lesions in vagina twice weekly for 12 weeks by a gynecologist. The patient complained common side effects from the treatment. They were fever and flu-like symptoms, local irritation in the vagina. The symptoms occurred within 12 hours after application of imiquimod and were relieved by taking NSAIDs.

Results: After the treatment new biopsies were taken from cervical and vaginal lesions. The histological findings are CIN 1 and VAIN 1. HPV test is still positive.

Conclusions: Imiquimod seems to be a promising and safe alternative treatment modality to standard surgical intervention for high grade CIN and VAIN, especially when is highly preferred to avoid risks of surgical treatment and preserve patient's fertility.

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#0085

24 - Cervical neoplasia

Association of a genetic variant in ATP-binding cassette sub-family B member 1 with risk of developing cervical cancer

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Background/Objectives: Multidrug resistance protein1 (MDR1) or ATP- binding cassette sub-family B member1 (ABCB1) gene is a membrane-associated protein which transports various molecules across extra- and intra-cellular membranes. It is reported to be associated with drug resistance. Here we investigated the association of a genetic variant, rs1128503, in ABCB1 in patients with cervical cancer. Multidrug resistance protein1 (MDR1) or ATP- binding cassette sub-family B member1 (ABCB1) gene is a membrane-associated protein which transports various molecules across extra- and intra-cellular membranes. It is reported to be associated with drug resistance. Here we investigated the association of a genetic variant, rs1128503, in ABCB1 in patients with cervical cancer.

Methods: DNA was extracted from 263 cases with and without cervical cancer patients and then genotyped by TaqMan real-time PCR. Logistic regression was utilized to assess the relationship between CC risk and genotypes. The significant prognostic variables in the univariate analysis were included in multivariate analyses.

Results: The genotypic frequency for GG, AG, and AA were 21.5%,62.7%,15.6% in the patient group and 14.6%, 52.8%, 32.5% in the healthy group respectively. Our data showed that the GG genotype was associated with the increased risk of cancer in the recessive genetic model. In particular, this analysis revealed that cervical cancer patients with GG genotype had an odd ratio (OR) of 2.6 (95%CI: 1.1-5.8, p=0.02) under a recessive model and OR of 2.46 (95%CI: 1-5.6, p=0.03: AG vs AA) in the additive model.

Conclusions: Our findings demonstrated the association of a genetic variant in ABCB1 gene with increased risk of developing cervical cancer, supporting further investigations in a larger and multi centre setting to explore the value of emerging marker for management of cervical cancer.

#0094

24 - Cervical neoplasia

OUR EXPERIENCES WITH DIAGNOSIS AND RESULTS OF CERVICAL PATHOLOGY TREATMENT.

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Background/Objectives: Background: Human papillomavirus (HPV) represents an etiologic agent of cervical premalignant lesions and carcinoma of the cervix. Our objective was to perform a 3 years' retrospective analysis of the correlation between cytology, colposcopy, histological and immunohistochemical examination within a group of women treated by cone biopsy of cervical pathology.

Methods: Material and methods. We carried out a study of 207 patients with pathological lesions of the cervix. Irregularity diagnoses were performed by cytology, colposcopy, histology and immunohistochemical staining, usually for p16 and Ki64. All 207 patients had undergone Fischer cone biopsy as a tool for diagnosis and therapy at our department. In some cases HPV determination was performed. We also observed a case of recurrence.

Results: Results: We detected 6 cases of microinvasive cervical carcinoma and 3 cases of adenocarcinoma. In 45 % of the cases we proved CIN 3. Negative histological results were observed in 10 % of the cases (usually metaplasia, hyperplasia and inflammation changes). On the other hand, discrepancies were observed between cytology and colposcopy and following histology in 4,3 % of the cases. In one case from this last group there was a cytological L SIL, colposcopy HG lesion and histological result was a microinvasive carcinoma. Recurrence of the disease occurred in 4,3 % of the cases.

Conclusions: Conclusion: In our study we proved a high reliability of the cervical pathology diagnostic methods. Histological and immunohistochemical examinations have an essential significance for the confirmation of the extent of the disease.

#0098

24 - Cervical neoplasia

DIAGNOSTIC PERFORMANCE OF P16/KI67 IMMUNOSTAINING IN COMPARISON WITH HPV DNA AND MRNA ASSAYS TO IDENTIFY HIGH GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA IN WOMEN WITH MINOR ABNORMAL CYTOLOGY. THE GREEK EXPERIENCE.

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Background/Objectives: Biomarkers showing the shift from self-cleared transient to potentially dangerous transforming HPV infections may improve the accuracy of cervical cancer screening. While ASCUS can be triaged with HR-HPV DNA testing to identify those who need a referral, LSIL cannot be triaged by HR-HPV DNA testing because of very low specificity. High levels of p16 + ki67 expression indicating persistent and transforming HPV infection may be a better predictor of underlying high grade cervical intraepithelial neoplasia or worse. We evaluated the value of p16/ki67 immunostaining, HPV E6/E7 detection in triaging women with ASCUS/LSIL in comparison with HPV DNA testing.

Methods: 280 women 21-65 yrs with minor abnormal cytology were subjected to Thin-Prep LBC sampling for analysis of HPV-related biomarkers. Detection rates of p16/ki67 immunocytochemistry (CINtec plus, Roche Diagnostics), HPV E6/E7 mRNA testing (APTIMA, Hologic) and HPV DNA testing (HPV Direct flow chip, Master Diagnostica) were evaluated in terms of histologically confirmed high grade cervical intraepithelial neoplasia or worse.

Results: Using CIN2+ and CIN3+ lesions as the gold standard, the sensitivities (SV), specificities (SP), and predictive values (PVs) for all tests were estimated. All HPV-related biomarkers yielded high SV for CIN3+ detection (94% for HPV DNA test and 96% for APTIMA & CINtec) and CIN2+ (90.8% for HPV DNA test, 91.6% for APTIMA and 88.3% for CINtec). The SP to detect underlying high grade dysplasia was highest for CINtec (60.8% in CIN3+ and 74.3% in CIN2+) while APTIMA HPV Assay and HPV DNA test had lower values (52.1% in CIN3+ and 62.5% in CIN2+ / 49.1% in CIN3+ and 56.2% in CIN2+ respectively) than CINtec plus. All tests had higher sensitivity using p16/ki67-IHC-positive CIN2+ lesions as endpoint. The positive and negative PVs for detecting an underlying CIN3+ lesion using the CINtec PLUS test were 34.7% and 98.5%, respectively while the corresponding PVs for APTIMA HPV Assay were 30.3% and 98.3% and HPV DNA test were 28.6% and 97.4%.

Conclusions: P16/ki67 dual staining in minor abnormal cytology demonstrated high SV similar to APTIMA mRNA assay for the detection of underlying high grade neoplasia and higher SP especially in CIN2+ detection.

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#0133

24 - Cervical neoplasia

Comparison of histological outcomes from pre-menopausal and post-menopausal women with report of cervical cytological abnormality

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Background/Objectives: The aim of this study is to compare and investigate the histological outcomes between premenopausal and post-menopausal women with report of cervical cytological abnormality.

Methods: From January 2010 to May 2018, patients with abnormal cervical cytology followed by histopathologic examination were collected from Department of Obstetrics and Gynecology of Haeundae Paik Hospital. The patients were divided into two groups according to menopause status and the histologic results of the two groups were compared. This study included the following cervical cytological abnormalities: atypical squamous cells of undetermined significance (ASC-US), cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL).

Results: The results of the cervical cytology among the 438 premenopausal women were ASC-US (n=91), LSIL (n=90), HSIL (n=193) and ASC-H (n=64). The results were ASC-US (n=12), LSIL (n=21), HSIL (n=63) and ASC-H (n=19) in 115 postmenopausal women. According to cytology results, we divide into the two group, ASC-US and LSIL were classified as low risk group, ASC-H and HSIL as high risk group. Within the low risk cytology group, HSIL was 73.5% (133/181) by histologic biopsy in the premenopausal group and 42.4% (14/33) in the postmenopausal group. This was 88.7% (228/257) in the premenopausal group and 70.7% (58/82) in the postmenopausal group within high risk cytology group. In both comparisons, there was a statistically significant difference between premenopausal and postmenopausal women.

Conclusions: In conclusion, our comparative study's findings showed significant difference in correlation of cytology and histology results from premenopausal groups and postmenopausal groups with cervical cytology abnormality. On the basis of this result, we think that since cytological results in postmenopausal women than premenopausal women have low sensitivity, follow up pap smear with high risk HPV testing would be a more conservative management and appropriate than immediate colposcopic biopsy. This may be more significant due to our aging population and as the proportion of older women participating in PAP smear is likely to increase in future.

CLEAR CELL CARCINOMA OF CERVIX: A CASE SERIES FROM A SINGLE CENTER

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Background/Objectives: Clear cell carcinoma(CCC) of cervix is extremely rare type of cervical adenocarcinoma in these days. Diethylstilbestrol(DES) was banned in 1970's after the documentation that CCC of female genital tract was strongly associated with intrauterine exposure of that. However, cervical CCC cases without DES exposure were reported constantly. Herein, we report 10 cases of cervical CCC experiences. The purpose of this research was to identify the clinical behavior and prognosis of surgically treated clear cell carcinoma of cervix.

Methods: We retrospectively identified 10 patients with cervical CCC who underwent radical hysterectomy in Asan medical center from 2009 to 2018. Data regarding clinicopathological factors and surgical and oncological outcomes following radical hysterectomy were extracted from medical records and analyzed.

Results: The median age was 48 years(range: 19-64 years) and none of the patients reported DES exposure. Four cases were stage I, three cases were stage II, two cases were stage III, and one case was stage IV disease. Five cases were open radical hysterectomy, and five cases were laparoscopic radical hysterectomy. No intraoperative complication was reported. There were two cases of bladder dysfunction and lymphocyst following surgery. Histologic parametrial invasion was not seen in all cases, three patients showed pelvic lymph node metastasis, and two patients showed para-aortic lymph node metastasis. One patient underwent neoadjuvant chemotherapy, five patients underwent adjuvant chemotherapy, and two patients underwent adjuvant concurrent chemoradiotherapy, and two patients had no adjuvant therapy. One patient had been recommended adjuvant chemotherapy, but became follow up loss. We confirmed her survival via national health insurance system although her disease status was unknown. Two deaths were reported, one was due to progression of disease during adjuvant chemotherapy, and the other was due to infected lymphocyst causing acute kidney injury. No recurrence was recorded during the study period, seven patients are still alive without disease, and one patient is alive with unknown disease status. Median follow up time was 43.8 months(range: 6.6-110.9 months), and 5 year survival rate was 80%.

Conclusions: Reported 5-year survival rates for patients with all stages of cervical CCC range between 40% and 64%. Stage, tumor size, growth pattern, nuclear atypia, and mitotic activity seem to be prognostic factors. Our series tended to have slightly better 5-year survival rate than previous data. In conclusion, we present case series of surgically treated CCC of cervix. Further studies are needed for profound understanding this rare entity of tumor.

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#0501

24 - Cervical neoplasia

TREND ANALYSIS OF CYTOLOGICAL ABNORMALITIES IN OPPORTUNISTIC CERVICAL SCREENING AMONG YOUNG WOMEN IN THE NETHERLANDS

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Background/Objectives: HPV vaccination was introduced in the Netherlands in 2009, starting with a catch-up campaign for 13- to 16-year-old girls. Thereafter girls were routinely offered vaccination in the calendar year they turned 13. HPV-vaccine eligible girls will enter the Dutch cervical screening program at 30 years of age, i.e. from 2023 onwards. However, it appears that every year a substantial number of young women before the age of 30 have a cervical smear test taken outside the regular screening program. In this study we used data of opportunistic screening to explore trends in cytological abnormalities and to indicate possible early effects of HPV vaccination.

Methods: Women younger than 30 years of age with a cervical smear test between 1995 and 2016 were selected from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). Trends of cytological abnormalities were explored over time and by age. In addition, vaccine-eligible cohorts and non-eligible cohorts were compared using Poisson regression correcting for age and calendar year.

Results: Annually, on average 42,500 (range 29,419 to 105,812) girls younger than 30 years of age (0.025% of the population) had a cervical smear test taken between 2000 and 2016. The percentage of pap2+ is increasing since 2001. The percentage also increases with age up to the age of 24 and thereafter declines again. The percentage of Pap3a2+ remained more or less stable up to 2006, but increased thereafter. The percentage of Pap3a2+ increases steadily with age.

Conclusions: In the Netherlands, the incidence of Pap2+ and Pap3a2+ in opportunistic cervical screening has increased over time since 2001. This increasing trend has not been halted by HPV vaccination yet, which is likely due to the rather young age of vaccine-eligible girls in the study period (i.e. up to 23 years of age) and the suboptimal vaccination coverage in the Netherlands (46-61%).

#0553

24 - Cervical neoplasia

Efficacy of collagen sealant for reducing hemorrhage after loop electrosurgical excisional procedure (LEEP)

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Background/Objectives: To assess the hemostatic effect of thrombin-collagen sealant (Collastat) use after loop electrosurgical excisional procedure (LEEP) of uterine cervix.

Methods: We retrospectively collected clinicopathologic data of 154 patients who underwent LEEP at our institute. Between Dec.2018 and Aug. 2019, 60 patients were managed with Collastat after LEEP (Collastat group, n=60). The LEEP for control group (n=94) was performed before 2018 and Collastat was not applied to these control group. We compared the incidence of severe bleeding which required any intervention for bleeding control within 30 days after LEEP.

Results: Clinicopathologic variables were similar between the two study groups. However, the incidence of severe bleeding was statistically different between the two groups. Severe bleeding occurred in 2 out of 60 patients (3.3%) in Collastat group, compared with 16 out of 94 patients (17%) in control group (p=0.01) Age, parity, resection margin status, and pathology result were not correlated with the incidence of severe bleeding after LEEP.

Conclusions: Use of Collastat may reduce the incidence of severe bleeding after LEEP.

#0232

26 - Vulvar diseases and neoplasia

Clinical feature and HPV prevalence in vulvar intraepithelial neoplasia

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Background/Objectives: Vulvar intraepithelial neoplasia (VIN) is an increasingly common problem, particularly among women in their 30s. Although spontaneous regression has been reported, VIN should be considered a premalignant condition. Clinical heterogeneity and uncertain natural history, relationship with HPV infection is still unclear, early diagnosis and appropriate treatment of VIN are essential.

Methods: Review and analysis of clinical characteristics, HPV prevalence and accompanying genital lesion of patients diagnosed with VIN in our institute in the past 5 years was performed

Results: Of 16 patients with VIN, 9 patients with high grade VIN(56%) and 7 patients with low grade VIN(44%) were observed. 3 patients with high grade VIN (33.3%) were asymptomatic. HPV DNA testing was performed in most cases, among 9 patients with high grade VIN, 5 had high risk HPV positive in cervicovaginal samples, four of five was HPV 16, among 7 patients with low grade VIN, five had HPV positive, one of five was HPV 16. Accompanying cervical or vaginal intraepithelial neoplasia(CIN, VAIN)were identified. Among 9 patients with high grade VIN, four had CIN(all HPV positive), in 7 patients with low grade VIN, four had CIN, one had VAIN and one had endometrial cancer. The most frequent symptoms were pruritus (43.7%), and pain or discomfort (32%). In 16 VIN cases, accompanying cervical or vaginal intraepithelial neoplasia or HPV infection was identified 12 cases. Wide local excision was performed in all cases of high grade VIN as a primary treatment. For seven low grade VIN, one patient with endometrial cancer previously treated with surgery and chemoradiation was treated with local excision. Six cases were followed up with no progression to high grade VIN. The mean follow-up period after treatment was 21.3 months, with a relapse rate of 22% in the high grade VINs. Recurrence was observed in two cases and treated with simple hemivulvectomy.

Conclusions: Since patients with VIN are often asymptomatic, vulvar inspection should not be overlooked during gynaecological examination, particularly in women with high risk HPV infection or CIN, VAIN. Prevalence of HPV infection in cervicovaginal samples patients in high and low risk VINs is not different but HPV 16 infection is more common in high risk VINs

#0221

26 - Vulvar diseases and neoplasia

PREVALENCE OF HPV AND P16 EXPRESSION IN VULVAR SQUAMOUS CELL CARCINOMA: A POPULATION-BASED DANISH STUDY OF >1,500 CANCERS.

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Background/Objectives: Approximately 30-40% of vulvar squamous cell carcinomas (SCCs) are estimated to be caused by human papillomavirus (HPV). However, studies of the HPV prevalence in vulvar SCC have shown heterogeneous results, and few have evaluated the combined HPV and p16 status. In this large, population-based study, we estimated the prevalence of HPV and p16 expression in vulvar SCC in Denmark.

Methods: In a nationwide pathology register, we identified all cases of vulvar SCC diagnosed at 13 pathology departments throughout Denmark during 1990-2017 (n=1,663). Formalin-fixed, paraffin-embedded blocks of tumor tissue from diagnostic biopsies or surgical excision specimens were retrieved from archives. The original diagnosis was reviewed by a pathologist at each department. Tumor blocks were sent to Vejle Pathology Department where sections were made for HPV testing and p16 immunostaining. HPV DNA testing was performed with the INNO LiPA HPV Genotyping Extra II test for 32 HPV genotypes, and p16 staining was performed using the CINtec histology kit. All p16 slides were read by two pathologists, and tumors with >70% tumor staining cells were considered positive.

Results: As of August 2019, results were available for 434 vulvar SCCs (26% of the total sample). The median age at diagnosis was 72 years (range 27-99 years). Of the included vulvar SCCs, 105 (24.2%) were keratinizing, 10 (2.3%) were non-keratinizing, 18 (4.1%) were warty/basaloid, 9 (2.1%) were verrucous carcinoma, and 292 (67.3%) were SCC not otherwise specified. A total of 235 cases (54.2%) were HPV DNA positive, with HPV16 being the most common type (n=161, 68.5% of the HPV positive tumors). The HPV prevalence was higher in warty/basaloid (13/18, 72.2%) than in keratinizing (40/105, 38.1%) tumors. The combined prevalence of HPV and p16 positivity was 30.4% (132/434), with higher HPV+/p16+ prevalence in warty/basaloid (11/18, 61.1%) than in keratinizing (15/105, 14.3%) tumors.

Conclusions: These preliminary results support that approximately 1/3 of vulvar SCCs are attributable to HPV infection, with a higher degree of HPV association in warty/basaloid than in keratinizing SCCs. Data collection for the study is ongoing, and updated results will be presented at the conference.

#0190

28 - Oral HPV infection

NATURAL HISTORY OF ORAL HUMAN PAPILLOMAVIRUS INFECTION IN HEALTHY POPULATIONS: Design of the PRevalence of Oral hpv infection, a Global assessment, THE PROGRESS STUDY

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Background/Objectives: Oral infection for human papillomavirus (OHPV) is associated with a subset of head and neck carcinomas. Natural history of OHPV, however, is not well known. Prevalence of OHPV in the general population is estimated to be 6.5% in Europe (1), 11.4% in the US (2), 0.6-0.8% in China and Japan (1;3) and seems consistently higher among men compared to women (4). OHPV prevalence variability may be due to differences in laboratory measures employed and study population characteristics. Less is known about the incidence, persistence and clearance of OHPV in the general population (5). The PROGRESS study aims to assess OHPV prevalence and associated risk factors among the general population in the US, France, Germany, Italy, UK, Spain, Japan and China. Incidence, persistence and clearance of the OHPV will be assessed prospectively in the US. This abstract describes the design of the PROGRESS study, which is ongoing.

Methods: A cross-sectional single cohort study in all eight countries, with a longitudinal follow-up in the US, will be conducted in dental offices. Public and private offices will be included in order to represent a more generalizable population. Dentists are healthcare providers that regularly provide oral health services to healthy populations and can readily collect an oral specimen. A total of 11,124 subjects (5,497 males, 5,627 females) including 2,968 in the US, 18 to 60 years of age, seeking routine dental care will be recruited. Subjects will be stratified by gender and age groups (18-30; 31-40; 41-50 and 51-60 years). All participants will provide written informed consent. At the baseline visit, the dentists will collect demographics and oral health information, and subjects will provide an oral rinse and gargle (ORG) sample, answer a behavior questionnaire (including risk factors and sexual behavior) and self-report HPV vaccination status. In the US, follow-up visits will occur every six months for up to two years. In each visit the ORG will be collected and behavior questionnaire re-administered. All analyses will be stratified by gender, age group, world region and HPV genotype. A multivariate regression model will assess risk factors independently associated with OHPV.

Results: N/A

Conclusions: Data arising from this study will inform the burden and natural history of OHPV among the general population across multiple geographic world regions utilizing a common standard protocol. Additional countries might be included in the future.

References: 1. Mena et al, J Infect Dis 2018; 2. Sonawane et al, Ann Intern Med 2017; 3. Hang et al, Cancer Epidemiol Biomarkers Prev 2014; 4. Kurose et al, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 5. Kreimer et al, Lancet 2013.

#0011

29 - HPV and oropharynx / Head and neck cancer

GENOMIC CHARACTERIZATION OF CLONAL EVOLUTION DURING OROPHARYNGEAL CARCINOGENESIS DRIVEN BY HPV 16

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Background/Objectives: Secondary prevention via earlier detection would afford the greatest chance for a cure in premalignant lesions. We investigated the exomic profiles of non-malignant and malignant changes in head and neck squamous cell carcinoma (HNSCC) and the genomic blueprint of human papillomavirus (HPV)-driven carcinogenesis in oropharyngeal squamous cell carcinoma (OPSCC).

Methods: Whole-exome (WES) and whole-genome(WGS) sequencing were performed on peripheral blood and adjacent non-tumor and tumor specimens obtained from eight Korean HNSCC patients from 2013 to 2015.

Results: Next-generation sequencing yielded an average coverage of 94.3— for WES and 35.3— for WGS. In comparative genomic analysis of non-tumor and tumor tissue pairs, we were unable to identify common cancer-associated early mutations and copy number alterations (CNA) except in one pair. Interestingly, in this case, we observed that non-tumor tonsillar crypts adjacent to HPV-positive OPSCC appeared normal under a microscope; however, this tissue also showed weak p16 expression. WGS revealed the infection and integration of high-risk type HPV16 in this tissue as well as in the matched tumor. Furthermore, WES identified shared and tumor-specific genomic alterations for this pair. Clonal analysis enabled us to infer the process by which this transitional crypt epithelium (TrCE) evolved into a tumor; this evolution was accompanied by the subsequent accumulation of genomic alterations, including an ERBB3 mutation and large-scale CNAs, such as 3q27-qter amplification and 9p deletion. We suggest that HPV16-driven OPSCC carcinogenesis is a stepwise evolutionary process that is consistent with a multistep carcinogenesis model.

Conclusions: Our results highlight the carcinogenic changes driven by HPV16 infection and provide a basis for the secondary prevention of OPSCC.

References: 1. Global Burden of Disease Cancer, Fitzmaurice C and Allen C (2016) Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2. Gooi Z, Chan JY and Fakhry C (2016) The epidemiology of the human papillomavirus related to oropharyngeal head and neck cancer. *Laryngoscope* 126, 894-900 3. Chaturvedi K, Engels A and Pfeiffer M (2011) Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 29, 4294-4301 4. Chaturvedi K, Anderson F and Lortet-Tieulent J (2013) Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol* 31, 4550-4559 5. Cancer Genome Atlas (2015) Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* 517, 576-582

#0134

29 - HPV and oropharynx / Head and neck cancer

A retrospective study of intra-arterial chemotherapy with concurrent radiotherapy for resectable locally advanced HPV-positive oropharyngeal carcinoma

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Background/Objectives: HPV is associated with carcinogenesis of oropharyngeal carcinoma. We report our experience with patients who received intra-arterial chemotherapy with concurrent radiotherapy for resectable locally advanced oropharyngeal carcinoma.

Methods: We reviewed 18 patients with a diagnosis of oropharyngeal carcinoma treated with intra-arterial chemotherapy with concurrent radiotherapy between February 2006 and April 2016. The patients were treated with 3 courses of cisplatin (100 mg at 1 treatment, intra-arterial) and sodium thiosulfate (28 g at 1 treatment, intravenous) once every 2 weeks during concurrent radiotherapy (66 to 70 Gy, 2 Gy per fraction, daily for 5 days over 7 weeks). Nodal metastases larger than 3 cm in diameter were treated with an additional 50 mg of cisplatin. The main outcome measures were overall response rate, overall survival (OS), and progression free survival (PFS). Moreover, we evaluated subsite-specific differences in survival between oropharyngeal carcinoma of the base of tongue (BOT) and palatine tonsil. The results are expressed as actuarial values using the Kaplan-Meier estimates.

Results: The median follow-up time was 24.6 months (range: 6.9-108 months). There were 15 males and 3 females with a median age of 67.5 years (range: 55-86 years). The tumors were staged by TNM classification (UICC 7th edition) as follows: Stage III 5 and Stage IV 13. They included 5 base of tongue, 12 palatine tonsil and 1 posterior wall patients. The actuarial overall survival rates at 2, and 5 years were 86.7 and 86.7 %, respectively. The actuarial progression free survival rate was 76.6 and 76.6 % at 2 and 5 years, respectively. The 5-year OS of BOT and lateral wall was 100 and 90.9 %, respectively. The 5-year PFS of BOT and lateral wall was 100 and 75 %, respectively.

Conclusions: This treatment regimen is effective option for advanced resectable oropharyngeal carcinoma.

#0186

29 - HPV and oropharynx / Head and neck cancer

THE INFLUENCE OF HUMAN PAPILLOMAVIRUS ON NASOPHARYNGEAL CARCINOMA IN JAPAN.

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Background/Objectives: Although Japan is a non-endemic area with nasopharyngeal carcinoma (NPC), the proportion of WHO type I NPC in Japan are different from that in non-endemic areas such as North America and Europe. Recently, not only Epstein-Barr virus (EBV) but also human papillomavirus (HPV) has an influence on NPC in non-endemic areas. The aim of this study is to investigate the influence of HPV on NPC in Japan.

Methods: Paraffin-embedded tumor specimens were available for 59 patients with NPC diagnosed between 1996 and 2015. We detected the virus status by p16 immunohistochemistry, HPV PCR, and in situ hybridization for EBV-encoded RNAs (EBERs). Of the 59 patients, 36 patients received radiotherapy with cisplatin-based concurrent chemotherapy. According to the change in treatment protocol from 2005, 18 patients received alternating cisplatin and 5-FU chemo-radiotherapy. Four patients received radiotherapy alone due to increased age (>70 years) or renal dysfunction. The accumulated dose of radiation to the nasopharynx was 70- 77 Gy in all cases, and the dose to the neck was 40-70 Gy. One patient refused treatment. The overall survival of the patients categorized by viral status was analyzed by Kaplan-Meier curves and Log-Rank test.

Results: Among the 59 patients, 49 (83%) were EBV-positive/HPV-negative, 2 (3%) were EBV- positive/HPV-positive, and 8 (16%) were EBV-negative/HPV-negative. All HPV-positive NPCs were co-infected with EBV. There were no statistically significant differences between the overall survival in the three groups ($p = 0.111$).

Conclusions: In Japan, HPV was detected in a few patients with NPC, suggesting that HPV has no influence on NPC carcinogenesis in this population.

#0218

29 - HPV and oropharynx / Head and neck cancer

Changes in incidence and prevalence of human papillomavirus in tonsillar and base of tongue cancer during 2000-2016 in the Stockholm region and Sweden

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Background/Objectives: To follow the incidence of human papillomavirus (HPV)-positive and HPV-negative tonsillar and base of tongue cancer in Stockholm during 2000-2016 in comparison to previous data. Tonsillar and base of tongue squamous cell carcinoma has increased. In Stockholm, the proportion of human papillomavirus (HPV)-positive cases and the incidence of tonsillar squamous cell carcinoma rose between 1970-2006 then stabilized. Here, HPV-prevalence, and tonsillar and base of tongue squamous cell carcinoma incidence 2000-2016, in Stockholm and Sweden were followed.

Methods: Incidence data for 2000-2016 were obtained from the Swedish Cancer Registry. Tonsillar and base of tongue cancer squamous cell carcinoma biopsies, 2013-2016 from Stockholm, were examined for HPV DNA and p16INK4a, or data obtained from medical reports. For cases 2000-2012, data were available from previous studies.

Results: The incidence of tonsillar and base of tongue squamous cell carcinoma incidence has continued to rise in Stockholm and Sweden 2000-2016, especially after 2008. HPV DNA and p16INK4a analysis was determined for 795 Stockholm cases from 2000-2016, with 72% being HPV DNA and p16INK4a positive 2013-2016, and 70% positive 2000-2016.

Conclusions: During 2000-2016, especially after 2008, the incidence of tonsillar and squamous cell carcinoma has continued to increase in Stockholm and Sweden, with an HPV-prevalence of ~70% in Stockholm.

#0270

29 - HPV and oropharynx / Head and neck cancer

Ectopic chromosome around centrosome (ECAC) as a potential marker of human papillomavirus (HPV) infection on oropharyngeal carcinoma

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Background/Objectives: The 8th edition of UICC TNM classification of malignant tumors, the latest revision, has been published in 2017, and human papillomavirus (HPV) status has been introduced to the classification of oropharyngeal carcinoma. However, immunohistochemistry of p16 or in situ hybridization of HPV DNA is required for determining HPV status. More cost and time effective method to detect HPV infection is expected. Furuta et. al has reported that ectopic chromosome around centrosome (ECAC) in metaphase cell nuclei, which is detectable on hematoxylin-eosin (HE) stained section, is a potential surrogate marker of high-risk HPV-associated cervical neoplasms. In this study, we evaluated whether ECAC is also a potential surrogate marker of HPV infection on oropharyngeal carcinoma specimens.

Methods: We included 47 cases of oropharyngeal squamous cell carcinoma which were diagnosed at our institute between 2000 and 2011 (age 62.5 ± 10.2 , 40 males, 7 females) to this study. We investigated HE-stained sections under a light microscope and evaluated whether they have ECAC. We detected HPV DNA by polymerase chain reaction (PCR) method and performed typing by HPV DNA array.

Results: Of the 47 cases, 21 were HPV positive, and 26 were HPV negative. Two cases were co-infected with HPV16 and 31, and the other HPV positive cases were infected with HPV16 alone. On 21 HPV positive cases, 14 were ECAC positive. 9 cases out of 26 HPV negative were ECAC positive. The difference was statistically significant ($p=0.029$, chi-square test). The sensitivity of HPV infection with ECAC was 66.7%, whereas specificity was 65.4%.

Conclusions: We demonstrated that ECAC is also a potential marker of HPV infection on oropharyngeal carcinoma, though sensitivity and specificity are not high enough. ECAC may be morphologic evidence of HPV-induced chromosomal instability, which implies detecting morphologic alternation of chromosome on HE-stained section might help determining HPV status on oropharyngeal carcinoma.

References: 1. Furuta R, et. al. 2003. Ectopic chromosome around centrosome in metaphase cells as a marker of high-risk human papillomavirus-associated cervical intraepithelial neoplasias. *Int J Cancer* 106:167-171. 2. Union for International Cancer Control (UICC). 2017. TNM Classification of Malignant Tumors (Eighth Edition)

#0466

29 - HPV and oropharynx / Head and neck cancer

Predictive value of 18F-FDG metabolic tumor volume and total lesion glycolysis for systemic metastasis in tonsil cancer

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Background/Objectives: In solid tumor, standardized uptake value(SUV) and 18F-FDG metabolic tumor volume (MTV), total lesion glycolysis (TLG) have been proposed as potential prognostic imaging markers for patient outcome. We hypothesized that patients who have large metabolic tumor volume of lymph node would more likely progress to systemic metastasis. To verify those hypothesis, we designed this study and investigated pre-operative 18F-FDG PET/CT and oncologic outcomes of patients who have been treated in our institution.

Methods: A retrospective review of the medical record of the patients who were diagnosed with squamous cell carcinoma(SCC) of tonsil and underwent surgery as primary treatment at our institution from 2006 to 2016. Patients were excluded patients if they already had systemic metastasis or previous treated history for head and neck cancer. Among those patients, we only included patients who showed lymph node metastasis in pre-operative evaluation. Finally 55 patients were included and we analyzed their medical records and SUV, MTV, TLG of primary tumor and lymph node by 18F-FDG PET/CT.

Results: Finally 55 patients were included and 7 patients showed systemic metastasis during follow up period after all the treatment. We divided these patients into two groups by the presence of systemic metastasis and compared PET/CT data including SUVmax, SUVpeak, MTV, TLG of primary tumor site and lymph node. In primary site, No significant difference of those parameters was detected between two groups. Mean value of SUVmax(8.18 vs 9.97), SUVpeak(6.45 vs 7.26) of lymph node also showed no significant difference but MTV(18.76 VS 36.07), TLG(89.94 vs 183.46) showed statistical difference between two group(p-value<0.05). ROC curve for systemic metastasis showed AUC as 0.584, 0.590 for MTV, TLG and cutoff value to predict systemic metastasis was calculated as 7.35 for MTV with sensitivity 71.4%, specificity 43.5% and 39.37 for TLG with sensitivity 71.4%, specificity 52.2%.

Conclusions: In lymph node metastasis patients, large volume of metabolic activity has significant correlation with systemic metastasis and in those patients, systemic chemotherapy should be considered to prevent metastatic event. From the result of this study, we could suggest the reference for systemic adjuvant therapy using 18F-FDG PET/CT .

#0492

29 - HPV and oropharynx / Head and neck cancer

ATTRIBUTABLE FRACTION OF HPV RELATED HEAD AND NECK CANCERS IN THE RECURRENT / METASTATIC SETTING. A LITERATURE REVIEW OF PH I-III CLINICAL TRIALS

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Background/Objectives: Head and neck cancers (HNC) are the 6th most common forms of malignancy worldwide, with recurrent/metastatic (RM) disease carrying the poorest prognosis (10-12 months median survival). HPV is an independent causative factor of cancers developed in the head and neck (HN) area, predominately at the oropharynx (OPX), associated with ~25% of all HNC cases in most of the literature. Men are at 3-5 times higher risk. For the RM disease, several reports prognosis appears almost equally poor for both HPV+/- cancers 1-3. Percentage of HPV+ RM HN cancers is an important parameter for estimating actual burden of HPV+ HNC. This study presents the attributable fraction (AF) of HPV+ RM HN cancers as captured in the descriptive data of last decade's Ph I-III trials.

Methods: We searched Clinicaltrials.gov for HN Ph I-III trials in "Completed, Active-Not recruiting, Unknown Status" initiated after 01 Jan 2010 until 04 May 2019. PubMed, CENTRAL & EMBASE databases were searched for related publications and ASCO / ESMO Journals of congresses for related abstracts using the corresponding NCT#. Studies selected had: available results on HPV fraction with RM patients enrolled, OPX was included in the HN sub-sites & investigational products (IPs) were intended for treatment.

Results: We identified 809 HNC trials of which 21 fulfilled the criteria (4 PhI, 13 PhII & 4 PhIII). HPV AF in HNC RM had been estimated in these 21 trials (reports ranging from 3.9% to 52.0%) involving 3,461 subjects with 24.9% of them being HPV+. Furthermore, in 10 of the 21 trials had Oropharyngeal cancer (OPC) specifically reported (with OPC ranging from 25.0 to 68.0 % of HNC). HPV AF in the OPC subset was estimated in these 10 trials (reports ranging from 20.0% to 88.9%) involving 390 subjects with 54.6% of them being HPV+.

Conclusions: HPV AF in the RM patients correspond to the HPV AF of total HNC cases being estimated around 25 % of HPV+ HNC. Specifically, for OPC, the HPV AF of RM OPC was estimated around 55%. The incremental trend of HPV+ HN cancers especially in developed countries, mainly driven by the increase in OPC, highlights the potential of primary prevention through vaccination. Research on the role of the vaccine in the prevention of HN cancers should be continued along with the expansion of HPV vaccination to boys.

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#0530

29 - HPV and oropharynx / Head and neck cancer

FAMILIAL ASSOCIATION OF OROPHARYNGEAL AND ANOGENITAL HPV-CANCERS IS CALENDAR-TIME DEPENDENT

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Background/Objectives: Human papillomavirus (HPV) infections are associated with oropharyngeal cancer (OPC). With tonsillar and base of tongue cancer the association with HPV is especially strong. The incidence of HPV-associated OPC has risen over time especially in males. We evaluated the over time risk of OPC in spouses of women with HPV-associated incident anogenital cancer.

Methods: The updated Swedish Cancer Family database with 16M individuals and cancer data from 1958 to 2015 was used. Its complete family links in approximately 4M nuclear families extend over the last 100 years. The 7th International Classification of Diseases (ICD-7) was used to identify cases with primary diagnoses of possibly HPV-associated in situ and invasive cancers of the following anatomical sites: cervix (171), vulva (1761), vagina (176, except 1761), anus (1541), tongue (141), tonsil (1450), oropharynx (145, except 1450). The relative risk (RR) estimates of familial OPSCCs were calculated comparing OPSCC incidence rates in male spouses of female anogenital cancer cases with OPSCC incidence rates in the general population of males.

Results: The RR estimates for tonsillar and base of tongue cancers increase over time in spouses of women with in situ cervical cancer or invasive anogenital cancer. From 1969-2001 to 2002-2015, the increase was two-fold (up to RR 2.2) for spouses (diagnosed with tonsillar/tongue cancer at 50 years of age or younger) of women diagnosed with in situ cervical cancer <50 years of age. In 2002-2015, RR of tonsillar/tongue cancer peaked at 9.4 (95% CI 1.8-50) for similarly aged spouses of women diagnosed with invasive anogenital cancer <50 years of age.

Conclusions: The familial association of OPC (most notably tonsillar and base of tongue cancers) in males and anogenital HPV associated cancers in women appears to be calendar-time dependent. This may be due to the increase of the population attributable fraction of HPV infections in OPC brought on by the earlier increase of HPV16 infections in the fertile-aged population.

#0669

29 - HPV and oropharynx / Head and neck cancer

DRH1 - Evaluating a blood-based marker for HPV16-induced tumors

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Background/Objectives: The past decade has seen a steady rise in the incidence of HPV-induced cancers. In the US, the number of HPV16-induced OPSCC has already overtaken cervical cancer. This study aims to assess the performance of a newly developed blood-based assay for the detection and post-treatment monitoring of HPV16-induced head and neck squamous cell carcinoma (HNSCC).

Methods: This non-interventional, prospective study included 34 HNSCC-patients and 1064 CRP-negative controls. Patient sera were obtained at the time of diagnosis and over a 28-month follow-up period after treatment initiation, resulting in a total of 166 samples for analysis. The samples were analyzed for the presence of anti-HPV16 L1 antibodies using a newly developed rapid test based on the HPV16-L1-specific monoclonal antibody clone DRH1. Samples obtained at the time of diagnosis were used to assess the sensitivity of the assay in detecting HPV16-induced oropharyngeal carcinoma. To confirm HPV status, tumor specimens were analyzed for the presence of HPV DNA and p16 expression. CRP-negative control sera were used to establish the diagnostic specificity of the assay.

Results: A total of 20 tumors were found to be positive for HPV16 DNA. 19 of these 20 were also tested positive with the immuno-assay used here (DRH1 antibody concentrations of 1,000-28,000 ng/mL), resulting in a sensitivity of 95%. The diagnostic specificity of the assay was found to be 99.36% in men and 99.29% in women over 30 years. The majority of the patients with confirmed HPV16-induced carcinoma showed a decrease in DRH1 antibody levels of 30-100% after treatment. A rise in DRH1 antibody levels from 2,750 ng/mL to 12,000 ng/mL was observed in one patient during follow-up and was followed by a clinical diagnosis of disease recurrence.

Conclusions: The presence of HPV16 L1 DRH1 epitope-specific antibodies in patient blood is an indicator for HPV16-induced malignant growth. The immuno-assay used here provides a promising tool to track treatment response and may be used for the early detection of disease recurrence.

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30 - HPV and associated skin diseases

DETERMINATION OF CAUSATIVE HUMAN PAPILLOMAVIRUS TYPE IN HISTOLOGICALLY CONFIRMED COMMON WARTS, BASED ON ESTIMATED VIRAL LOADS

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Background/Objectives: Assessment of HPV type-specific viral loads (VLs) has been suggested as reliable approach for determination of main etiological agent in common warts (CWs) in which more than one HPV type has been detected. In this study most probable causative HPV type was determined in fresh tissue specimens of histologically confirmed CWs with single and multiple HPV infections, based on estimated VLs of the most prevalent common wart-associated Alpha- (HPV2/27/57) and Mu-PV types (HPV1/63/204).

Methods: Fifty-three and 71 DNA isolates from 93 patients with single and multiple HPVs, respectively, were analyzed for VLs with type-specific quantitative multiplex HPV2/27/57 real-time PCR (RT-PCR), allowing detection and differentiation of HPV2, 27 and 57 in a single PCR reaction, and three different type-specific quantitative Mu-PV RT-PCRs. Type-specific VLs, expressed as ratios between the number of viral copies and human diploid cells, were estimated based on the concentrations obtained with type-specific quantitative RT-PCRs and quantitative 150-bp beta-globin RT-PCR, respectively.

Results: In 53 CWs with single HPV infections, median HPV2/27/57 DNA VLs were estimated to 3.2×10^4 , 2.8×10^4 and 1.8×10^4 viral copies/cell, respectively, and were significantly higher compared to estimated VLs of HPV1 (8.2×10^{-3} viral copies/cell) and HPV63 (2.0×10^{-3} viral copies/cell). No single HPV204 infection was detected. Consequently, the most frequent etiologically associated HPVs in CWs with single HPV infections were HPV57, 27, and 2 with an overall prevalence rate of 77.3% (41/53), followed by HPV1 (3.8%, 2/53). HPV63 was not determined as an etiological agent in any of these CWs. In 71 CWs with multiple infections, HPV2/27/57 VLs ranged from 6.0×10^{-4} to 3.6×10^5 viral copies/cell, whereas VLs of HPV1/63/204 ranged from 7.0×10^{-4} to 1.6×10^2 viral copies/cell (generally lower than 1 viral copy/cell). The most prevalent causative agents of CWs with multiple HPVs were HPV57, 27, and 2 with an overall prevalence rate of 74.7% (53/71), followed by HPV1 (4.2%, 3/71). HPV63 and HPV204 were not determined as potential etiological agents in any of the CWs with multiple HPVs. In 10/53 and 15/71 CWs with single and multiple HPVs, respectively, causal agent could not be reliably determined.

Conclusions: No significant differences in VLs of disease-causing HPV types in CWs with single and multiple HPVs were found. In the majority of CWs with multiple HPVs, single dominant HPV type was present with a very high VL, indicating etiological association.

31 - Genital warts

CHARACTERISTICS OF HUMAN PAPILLOMAVIRUS 6 AND 11 INFECTION IN ANOGENITAL WARTS AND CORRESPONDING HAIR FOLLICLES OVER THE PERIOD OF TWO YEARS

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Background/Objectives: To determine whether in a cohort of men, prospectively followed-up every three months for up to two years, identical human papillomavirus (HPV) 6 and 11 viral variants were present in anogenital warts (AGW) and corresponding hair follicles and, additionally, to ascertain whether the identified viral variants were persistent and/or associated with the greater likelihood of disease's recurrence.

Methods: At each sampling point, the present AGW and at least 5 hairs were obtained from three anogenital sites (scrotal, pubic and perianal) and eyebrows of each of the 32 male patients, treated according to international standards. Additionally, five hairs per sampling site were obtained from each of the 32 healthy sexually active male volunteers, with no history of AGW, which were matched to cases by age, age at first sexual intercourse, sexual orientation, number of lifetime sexual partners, circumcision, condom use and shaving of the anogenital area. Following DNA extraction, samples' integrity was verified by beta-globin real-time PCR (RT-PCR) and DNA isolates were further tested for the presence of HPV using HPV6/11 RT-PCR and GP5+/6+/68 PCR. HPV6 and 11 viral variants were determined based on the 960- and 208-bp representative regions for whole-genome-based phylogenetic clustering (J Virol 2014;88:7307-16, J Virol 2016;90:5503-13), using newly developed type-specific PCRs.

Results: Altogether, 49 different AGW were collected at initial medical examinations of all patients, with AGW most frequently occurring on the penis (24/49; 49.0%), followed by pubis (15/49; 30.6%), scrotum (5/49; 10.2%) and perianus (5/49; 10.2%). All initial AGW harbored infections with single HPVs, with HPV6 (28/32; 87.5%), HPV11 (3/32; 9.4%) and HPV40 (1/32; 3.1%). In 81.3% (26/32) of patients, at least one initial pool of hairs was HPV-positive. Furthermore, all HPV6 (n=14) and HPV11 (n=1) viral variants, detected in hairs of a single patient, were identical to initial and all follow-up AGW samples. Based on the characteristics of HPV6 infection, patients were further divided into three groups (cleared HPV infection: n=15, persistent HPV infection: n=7, recurrent HPV infection: n=6). Taken together, three and two distinct HPV6 viral variants were present only in samples of patients with persistent infections and recurrent AGW, respectively. No HPV-DNA was detected in samples of the control group.

Conclusions: Even though identical HPV6/11 viral variants persist in AGW/corresponding hairs for up to two years, the mechanisms of AGW recurrence still warrant further studies on a larger sample size.

#0076

35 - Advocacy, acceptability and psychology

SAFETY FIRST: ELDERLY WOMEN'S EXPERIENCES WITH HPV TESTING, CYTOLOGY AND COLPOSCOPY, AND VIEWS ON PREVENTIVE TREATMENT FOR CERVICAL CANCER.

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Background/Objectives: Screening has significantly reduced the incidence and mortality of cervical cancer. However, not much is known about older women's preferences in terms of follow-up and treatment of abnormal screening tests. It is well known that the sensitivity of cervical cytology and the performance of colposcopy decline with age, particularly because of the retraction of the transformation zone into the cervical canal. Thus, to obtain sufficient biopsies and an accurate diagnosis, a strategy could be to perform a diagnostic cone biopsy if colposcopy is unsuccessful. However, this strategy may pose a significant risk of overtreatment. In this study, we aimed to assess older women's experience with colposcopy and their views on preventive treatment for cervical cancer precursor lesions and to identify preferences and unmet needs.

Methods: We conducted a qualitative interview study with women aged 60 years or older in four focus groups. All participants had a record of an abnormal smear (i.e. either HPV positive or ASCUS+) and had undergone a colposcopy; some women also had a cone biopsy. A dynamic semi-structured interview guide was used, and interviews were audio-recorded and transcribed verbatim. A thematic analysis was conducted, based on an interpretive tradition of ethnography.

Results: Five main themes were consistent throughout the interviews; 1. A concern about timely follow-up after abnormal results at the general practitioner. 2. The women preferred direct referral to colposcopy over regular HPV testing in general practice. 3. They called for thorough oral and written information before colposcopy. 4. A wish for an unambiguous oral recommendation from the gynecologist regarding treatment options. 5. The majority of the women preferred a diagnostic cone biopsy ('see and treat') despite a high risk of overtreatment

Conclusions: Adequate written and oral information about potential follow-up and treatment options for abnormal smears was important for older women. The women preferred a clear recommendation from their gynecologist about the best treatment or follow-up option. They emphasized that getting an accurate diagnosis was important to them, even though this may require a diagnostic cone biopsy, a procedure that may turn out to be unnecessary.

#0293

35 - Advocacy, acceptability and psychology

INCREASING SCREENING UPTAKE: TRAINING JAPANESE NURSES TO PERFORM CERVICAL SCREENING

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Background/Objectives: Annual cervical screening began in the 1960s in Japan for women >30yrs. From 2004, age was lowered to 20yrs and screening interval increased to biennially. However, uptake is poor at around 30-40% and even lower in women in their 20s. HPV vaccination uptake is <1% so Japanese women remain at an unacceptable risk for cervical cancer. Reasons for not attending screening include embarrassment and resistance to male doctors. Until 2016, only doctors were legally permitted to perform screening. However, due to a shortage of Obgyn, especially in rural areas, in April 2016 a law was passed to allow nurses to perform screening. Resistance from medical societies has been strong and no training program developed for nurses. Given this situation, a multidisciplinary group of female health professionals devised and implemented a cervical screening program for nurses. This study aims to outline and report on the first intake of participants.

Methods: Snowball sampling was used to recruit participants. The program took place over three days in two cities. It consisted of two parts; theory and practical. Lectures were given on: history of and issues with the Japanese screening program; overview of Japanese cervical screening guidelines; role of screeners and nurse-specific care accompanying gynecological examinations; anatomy and physiology of pelvic organs; interpretation and understanding of cytology results; health education and its role in screening uptake; and global HPV vaccine implementation and how it affects screening. For the practicum, participants practiced speculum use on models before practicing on other participants. While the main evaluation was cytology to ascertain cells from the transition zone had been adequately collected, HPV testing was also performed if the participants agreed to pay for this. The program was evaluated as follows: changes in knowledge about cervical cancer; accurate sampling; and knowledge of legal changes regarding screeners.

Results: Totally, 19 nurses enrolled and 17 did the practicum. Reasons for participating included: desire to contribute to improving women's health, increase screening uptake, and professional development. Correct knowledge about cervical cancer increased from 70% to 95% and there were no inadequate smears. Nurses felt confident they could perform screening.

Conclusions: No inadequate smears were taken and knowledge increased significantly. This suggests Japanese nurses may have an important role to play in increasing screening uptake and reducing the burden of cervical screening in Japan. However, training sites need to be increased and recognition from medical societies is necessary.

#0410

38 - Public health

EVOLUTION OF THE HPV VACCINE COVERAGE IN FRANCE: A FRENCH CLAIMS DATA STUDY

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Background/Objectives: Disparities of human papillomavirus infections (HPV) vaccine coverage rates (VCR) exist between European countries, and while HPV vaccination was introduced in the French vaccine schedule from 2007, French women seem to have one of the lowest VCR with around 30% of girls aged 15 receiving at least 1 dose (1). The PAPILLON study aimed to describe the evolution of HPV VCR with either bivalent, quadrivalent or nonavalent vaccines in the overall French population between 2017 and 2022, and to describe patients with one or several doses of HPV vaccine in terms of socio-demographic characteristics and healthcare resource utilization. Results from the 1st interim analysis are presented.

Methods: All patients recorded in the SNDS (Système National des Données de Santé, covering more than 98% of the French population) and having received ≥ 1 dose of HPV vaccine in 2017, were included. The whole vaccinated population was described and quantified. Calculations of VCR were carried out on the population of girls aged between 11 and 23 years at the time of first vaccination that are targeted by the recommendations of the French health authorities. Claims data of all HPV vaccines were collected from 2016.

Results: In 2016, 5.0%, 8.4%, 8.1% and 8% respectively of girls aged 11, 12, 13 and 14 (target population), initiated HPV vaccination (HPV vaccine initiation rates). HPV vaccine initiation rates were 7.3 % and 6.6% resp. in girls aged 15 and 16. Between 2016 and 2017, HPV vaccine initiation rates increased among girls aged 11 to 14 years (+0.5), while they slightly decreased again at 15 and 16 years old (-0.3). In 2017, the peak of initiation was at 12 years (9.0%). Prescribers of the initiation dose were mostly general practitioners. In 2016, 26.3% of the cohort of girls aged 15 years received at least one dose of HPV vaccine, they could have been vaccinated at 15 years old or before. This cumulative HPV vaccination rates for partial scheme (at least one dose) increased between 2016 and 2017 at 15 years old to reach 28.4%. When comparing non-vaccinated girls vs those who initiated HPV vaccination at 11 and 14 years old, the likelihood of receiving HPV vaccine increased with the number of visits to GP, gynecologist, pediatrician or hospital practitioner.

Conclusions: Our findings showed that HPV vaccination coverage is low in France but is currently increasing as observed between 2016 and 2017. Longitudinal follow-up will provide updates of these VCR until 2022. People having more contacts with health services seem to be more aware of the importance of prevention, and therefore of vaccination.

References:

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#0426

38 - Public health

KNOWLEDGE AND ATTITUDES TO HPV VACCINE IN A GROUP OF WOMEN WHO PARTICIPATED ON A CERVICAL CANCER PREVENTION CAMPAIGN

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Background/Objectives: Cervical cancer (CC) is the fifth cause of death for cancer in women worldwide and the incidence is 570.000 cases per year. 4484 new cases are diagnosed approximately every year and 2231 women die due to this pathology in Argentina. The HPV vaccine was incorporated into the national vaccination calendar in 2011, aimed to 11-year-old girls who have been born since 2000. Since 2017 it has been extended to 11-year old boys and it is also offered to boys and girls between 11 and 26 years old living with HIV and those who have been transplanted (solid organs or hematopoietics cells). In 2014, the transition from bivalent to quadrivalent vaccine was defined, with the additional benefit of preventing genital warts. The objective of this study was to determine the knowledge and attitudes towards HPV vaccination within women between 25-65 years old.

Methods: A cross-sectional study was conducted in a population of women who attended a CC screening campaign, during March 2019 in our unit. We included 811 women aged 25 to 65 who completed an anonymous questionnaire that included questions about knowledge and application of the HPV vaccine, and if their sons and daughters had received the HPV vaccine, according to the National vaccination program. In addition, patients' age, nationality, educational level, knowledge about the HPV virus, and the protection against it (condom and/or vaccine) were considered.

Results: 811 anonymous surveys of different nationalities were analyzed. The median age of the study population was 43 years (25-65 years). 62% were argentinian, the rest of the patients were from other countries: Peru, Bolivia, Brasil and Venezuela. 64.2% of respondents reached basic education. 269 women (33,1%) knew about the HPV vaccine as a method of prevention, while 33,9% thought that condom was enough. 319 had children who had been born after 2000, but only 140 cases (43,9%) were vaccinated.

Conclusions: The patients' level of knowledge about Cervical Cancer and vaccination against HPV in this study was found to be poor, in spite of both the achieved educational and socioeconomic levels; similar results can be seen in other countries with comparable development. This reflects the importance of an immediate implementation of educational campaigns throughout the country to enhance the adherence and awareness of the vaccination.

#0457

38 - Public health

MODELLING FOR PREDICTORS OF KNOWLEDGE SCORE ON AETIOLOGY AND PREVENTION STRATEGIES FOR CERVICAL CANCER AMONG WOMEN OF REPRODUCTIVE AGE IN IBADAN

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Background/Objectives: Cervical cancer is the commonest female genital tract cancer associated with high mortality and morbidity in developing countries. The high mortality had been associated with the poor knowledge of at-risk population, which directly impact on their health seeking behaviour towards this disease. Cervical cancer is preventable with vaccine and screening for premalignant lesions. Nigeria records 14,943 new cervical cancer cases and 10,403 related deaths every year, accounting for 27.2% and 20.0% respectively, of all cases in West Africa sub-region. This study aims to evaluate the knowledge of women on the causes, risk factors and prevention strategies of cervical cancer

Methods: A cross-sectional study that involved a multi-stage systematic sampling of 1002 women of reproductive age (18-49 years) in Ibadan. Knowledge of causes of cervical cancer were evaluated with 13 question items, and strategies to prevent cervical cancer were assessed with 9 questions. The responses were classified as "Yes", "No" or "Not sure". The score was assigned 1 for correct response and 0 for wrong answer. Knowledge on causes of cervical cancer was graded as 0 "No knowledge", 1-4 "poor knowledge" and 5-maximum as "good knowledge". Similarly, knowledge on prevention was scored as 0 "No knowledge", 1-4 "poor knowledge" and 5-maximum as "good knowledge". Test of association to determine factors associated with knowledge score for causes and prevention strategies of cervical were performed with ordinal logistic regression model.

Results: The median age of participants was 29.0years (range=23.0-35.0years), and they were mostly married. The median knowledge score of participants on causes and prevention strategies of cervical cancer was 3/13(0-4.0) and 3/9(0-5), respectively. Muslim (OR=0.61; 95% CI: 0.40-0.92), having multiple sexual partners (OR=0.64; 95% CI: 0.43-0.95) and access to previous counselling opportunity on cervical cancer screening (OR=0.34; 95% CI: 0.15-0.80) were less likely to have knowledge on causes of cervical cancer whereas respondents with higher income greater than 25000 Naira (OR=1.60; 95% CI: 1.01-2.56) were more likely to have knowledge about causes of cervical cancer. On factors associated with knowledge of prevention strategies of cervical cancer, ethnic groups other than Yoruba (OR=0.60; 95% CI: 0.40-0.90) and respondents with multiple sexual partners (OR=0.52; 95% CI: 0.33-0.83) were less likely to have good knowledge whereas respondents who were unskilled worker (OR=3.19; 95% CI: 1.08-9.40) and higher income greater than 25000 Naira (OR=1.94; 95% CI: 1.21-3.12) were more likely to have good knowledge about strategies to prevent cervical cancer.

Conclusions: The knowledge of women on risk factors, causes and prevention strategies of cervical cancer was poor. It is also worrisome that the poor knowledge was common among women with potential demographic risk factors for cervical cancer. We recommend innovative community mobilisation of women on risk factors associated with cervical cancer and prevention strategies.

References: Nil

#0533

38 - Public health

JAPAN AND UK COLLABORATION TO SUPPORT HPV BASED INTERVENTIONS FOR THE PREVENTION OF CERVICAL CANCER

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Background/Objectives: Research has shown that effective integration of human papillomavirus (HPV) immunization programs and HPV-based screening programs can eliminate cervical cancer as a public health problem in most countries by the end of the 21st century. Despite implementation of a successful HPV vaccination program in the UK, incidence of cervical cancer in unvaccinated age cohorts has started to increase. One important factor is a decrease in screening coverage. Groups most at risk include women of low socioeconomic status, women not born in the UK, and younger age. In Japan, cervical cancer is increasing in women of reproductive age and neither HPV vaccination, nor screening coverage meet WHO cervical cancer control targets. Measures to support HPV based interventions for the prevention of cervical cancer in both countries are necessary. This project, funded by the UK Sasakawa Foundation, aims to generate new knowledge by combining experiences and expertise from both countries to explore policy, program implementation, and cultural factors impacting participation in cervical cancer control programs.

Methods: In collaboration with the Scottish HPV Investigators Network (SHINe), a multi-disciplinary group which benefits from the expertise of clinical, public health, scientific, lay and government involvement, academic symposia will take place at Edinburgh University in the UK Hokkaido University in Japan. Presentations of lessons learnt will be made. Additionally, public lectures for expatriates in both countries will also be held in collaboration with the UK Embassy in Tokyo and the Japanese Consulate in Edinburgh

Results: A pooling of resources and information on the project webpage will be made available to assist and help find a way for other countries facing similar issues. Culturally sensitive bilingual patient information leaflets on screening and vaccination to facilitate access to cervical cancer control programmes in both countries will be developed. Finally, key findings will be disseminated at international HPV meetings and forums including Women Against Cervical Cancer (WACC).

Conclusions: It is hoped the project will result in a more comprehensive understanding of factors behind hesitancy to participate in cervical cancer control programmes in Japan and the UK. This information will help guide interventions that will have a significant impact on the lives, well-being and fertility of women in both countries.

#0756

38 - Public health

TOPICAL THERAPEUTIC DRUGS ARE ESSENTIAL TO REDUCING THE EXTREME GLOBAL DISPARITIES IN HUMAN PAPILLOMAVIRUS DISEASES AND DEATHS

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Background/Objectives: HPV diseases are responsible for 0.8% of human deaths and 5% of cancer deaths. HPV vaccines are safe and effective at blocking infections by nine viral genotypes. However, anticipation that prophylactic vaccines would substantially reduce the staggering burden of HPV diseases has been unfulfilled. Although HPV vaccines have been marketed since 2006, less than 1.5% of the world's population is vaccinated, primarily in high-income countries. Behind this disappointing uptake are bottlenecks in manufacturing and delivery, high cost, lack of public health infrastructure, anti-vaccine efforts, and competing economic and medical issues. Despite philanthropic and WHO initiatives in low- and middle-income countries where 85% of life-threatening HPV diseases occur, population growth is outpacing vaccination by 10-fold. The absolute number of at-risk people is growing, not declining.

Methods: Over-zealous support for vaccination has crippled efforts at alternative approaches to HPV management. Pathological evaluations and surgical interventions are out-of-reach in much of the world. Immunotherapies have so far proven elusive, likely due to immune-escape functions of HPV oncoproteins E6, E7 and E5. Ideally, HPV diagnoses should be followed immediately with self-administered topical treatments using effective, safe, well-tolerated and affordable small molecule antivirals. Early treatment of active lesions will reduce sexually transmitted infections and have immediate emotional and economic benefits, while suppression of persistent infections will require periodic screening for oncogenic HPV infections using low-cost, sensitive and predictive molecular tests.

Results: Our lab created 3-dimensional epithelial tissue cultures that enable robust productive infection cycles of high-risk HPV-18. We also have 3D raft models of HPV dysplasias and cancers. We repurpose existing drugs that cleared clinical trials for other indications. We have validated several anti-HPV agents of different pharmaco-chemical classes which are now in clinical trials, including ODE-Bn-PMEG (Antiva); Vorinostat (HDAC inhibitor of replication); and Novan-1000 (a macromolecule that releases nitric oxide). Small molecule-based therapies provide the most promising path forward to diminish health disparities in HPV diseases that disproportionately impact economically challenged communities and countries.

Conclusions: N/A

#0529

38 - Public health

HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE AND GENOTYPES DISTRIBUTION IN THE GENERAL FEMALE POPULATION OF SOUTHERN CROATIA (DALMATIA COUNTY)

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Background/Objectives: Very little is known about prevalence and distribution of HPV types in Croatia. There are only few studies, based on laboratory test results, related to cervical samples of selected women, referred by their gynecologists to laboratory for HPV DNA testing, with either normal or abnormal Pap smear. The aim of this study was to determine the prevalence of HPV and HPV genotypes distribution in the general female population of Southern Croatia (Dalmatia County).

Methods: We performed a prospective study about HPV prevalence and type distribution of outpatient women. Data were collected during routine check-up exams by an unaffiliated group of gynecologists across the County. Biases were eliminated because the gynecologists sent samples for HPV testing of all those women who came for regular gynecological examination on specific predetermined days over a period of one year. Women were excluded if they suffered from more severe diseases (e.g. carcinoma, immunodeficiency). HR HPV was detected in cervical exfoliated cells, by using a real-time FDA approved PCR assay (Cobas 4800 HPV Test) based on concurrent individual genotyping for HPV-16 and HPV-18 and pooled detection of 12 other HPVs.

Results: A total of 900 women aged 16-74 years, attending routine gynecological visits, were evaluated. 105 (11.66%) of them were HR HPV positive. Out of total of number of tested women, 252 (28%) were ≤ 29 years old and 648 (72%) were ≥ 30 years old. HR HPV infection was higher in women aged ≤ 29 years (57/252 (22.6%)) in compare with group older than 30 years (48/648 (7.4%)). Among 105 HPV positive samples, following genotype distribution was detected: HPV-16 in 34%, HPV-18 in 6.6% cases, while the other HPV types were established in 80% of positive samples. Multiple HPV infections were found in 25% of positive specimens.

Conclusions: Data from this study on the prevalence and distribution of HPV genotypes in general female population of southern Croatia could be valuable for better organization of HPV-based cervical cancer screening and vaccination programme in this region and in Croatia.

#0425

39 - Fertility and HPV

Human Papillomavirus Infection in Men from Couples Treated for Infertility and Its Impact on Fertility Outcome

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Background/Objectives: Human papillomaviruses (HPVs) are agents of a common sexually transmitted disease that are important factors responsible for cancer development and very probably infertility. HPV was found along the whole male genital tract including semen where it is bound to sperm cells. Spermatozoa infected by HPV are able to penetrate the oocyte and transfer HPV into hamster eggs. That is why there is a growing interest in the impact of HPV on male infertility. In this study, we aimed to assess the HPV prevalence in semen samples in male partner from couples treated for infertility and in cervical swabs of their female partner and its impact on fertility outcome.

Methods: Cervical swabs and semen samples from 399 female and male partners treated for infertility were collected between July 2013 and November 2016. All study participants provided signed informed consent for the use of their collected samples and completed a questionnaire on their health status and sexual behavior. All samples were analyzed for the presence of 14 hrHPV genotypes by cobas 4800 HPV system (Roche) than genotyped using PapilloCheck HPV-Screening system (Greiner Bio-One) which detects 18 hrHPVs. The association between hrHPV positivity and clinic characteristics was assessed using statistical software "R".

Results: HrHPV genotypes were detected in 16.3% (67/399) of women and in 8.77% (35/399) of men from infertile couples ($P = 0.001$). Both partners were hrHPV positive in 2.26% (9/399) of couples treated for infertility. The pregnancy rate in couples treated with IVF (98/161, 60.9%) and couples treated with IUI (27/53, 50.9%) was comparable ($P = 0.267$). The abortion rate in spontaneously pregnant women (5/46, 10.9%), couples treated with IVF (6/98, 6.12%), and couples treated with IUI (1/27, 3.70%) was not significantly different ($P = 0.489$). No associations between hrHPV infection of male, female or both partners and lower pregnancy rate or higher abortion rate were identified in couples treated for infertility regardless of the way of conception. Furthermore, no association of hrHPV positivity with fertility outcome was confirmed by multivariate analysis except the trend in reduction of pregnancy rate in HPV-positive women with unexplained infertility ($P = 0.094$).

Conclusions: HPV is well known key risk factor for cancer development and probably negatively influences fertility. Despite we did not find any significant association between hrHPV DNA semen presence and fertility outcome the data suggest that HPV infection probably reduce the rate of spontaneous pregnancy. This work was financially supported by IGA LF_2019_003, CZ.02.1.01/0.0/0.0/16_019/0000868, and LM2015064.