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SHARED CHALLENGES OF HPV DRIVEN CANCERS
FROM RESEARCH TO PRACTICE

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

ABSTRACTS

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#5011

Cartilage-hair hypoplasia (CHH) and risk for HPV related lesions

02 - Viral and molecular biology

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Background/Objectives: Ellonen, Schilling, Arponen, Vakkilainen, Mäkitie, Laine, Rautava Cartilage-hair hypoplasia (CHH) and risk for HPV related lesions Background: Cartilage-hair hypoplasia (CHH) is a rare chondrodysplasia with associated primary immunodeficiency. The aim of this cross-sectional observational study was to examine human papillomavirus status in individuals with CHH compared to their matched healthy controls.

Methods: Methods: Oral brush samples were collected from 23 individuals with CHH (4.5-70 years old) and of their 46 matched-controls (5-76 years old). Nested PCR approach followed by bead-based bead-based hybridization assay for Detection and Typing of 43 HPV types (13 high-risk, 10 possible high-risk, 20 low risk/non-classified) of the genus alpha was used as previously described (Schmitt et al., 2006, Kreuter et al., 2010). In addition, beta-, gamma-, mu- and nu- HPV types were analyzed (Berkhout et al., 1995, Li et al., 2013).

Results: Results: Of the samples with typeable results, 8/19 (42%) CHHs and 13/39 (33%) were positive for alpha HPV. The HPV types for CHH patients were HPV16, HPV27, HPV28, HPV78 and for controls HPV3, HPV16, HPV27, HPV61. For beta HPVs positivity was detected for 2/19 (10.5%) CHHs and for 2/39 (5.1%) controls. Combined presence of beta/gamma/mu/nu HPV types was found in 2/19 (10.5%) CHHs and in 1/39 (2.6%) controls. The statistical analysis is on-going.

Conclusions: Conclusions: CHH patients with primary immunodeficiency, showed increased prevalence of HPV DNA on their oral mucosa than their matched healthy controls. Therefore, they may be at increased risk for HPV related lesions and disease on the head and neck region.

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#5233

Prevalence of HPV-16 variants in the anogenital region of men: The HIM Study

03 - Epidemiology and natural history

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Background/Objectives: HPV-16 causes approximately 90% and 50% of anal canal and penile cancers, respectively. Globally, HPV-16 variant distribution is uneven and associates with the admixture level of each population. We and others have shown that women infected with HPV-16 sublineages A4 and D2/D3 variants are at a higher risk for cervical lesion. However, little is known regarding the prevalence of HPV-16 variants in the anogenital region of men. Our aim was to evaluate the prevalence and distribution of HPV-16 variants in the genitalia and the anal canal of men from three different countries (Brazil, Mexico and United States) enrolled in the HPV Infection in Men (HIM) Study.

Methods: The HIM Study was a longitudinal, prospective study which included 4,074 men across the USA, Brazil, and Mexico followed-up for four years. Men who had at least one HPV-16 positive anal canal or genital swab were included. Characterization of HPV-16 genetic variants was performed by PCR-sequencing a fragment of the viral Long Control Region (LCR).

Results: HPV-16 variant characterization was performed in 1,700 genital swabs from 753 men in addition to 217 anal canal samples obtained from 115 men. Overall, we observed a higher prevalence of lineage A variants (mainly from the A1 sublineage) both at the genitals (90.8%) and the AC (85.8%). HPV-16 variants from lineages B/C were detected in 5.7% and 7.5% of genital and canal samples, respectively; and the prevalence of lineage D variants was higher at the genitals (9.8%) in comparison to the anal canal (6.7%). Non-A lineage variants were mostly detected in both anatomical sites among men from Brazil, where a higher diversity of sublineage variants was also observed. Interestingly, among genital samples, C and D lineages variants were more commonly detected in Brazil (20·8%) than in the USA (9·8%). In contrast, lineage B variants were more commonly detected among men enrolled in the USA (4.3%).

Conclusions: Our data extend previous reports which indicate that globally HPV-16 variants are unevenly distributed and contribute further to studies of the natural history of HPV infections in the anogenital region of men.

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#4980

Duration of an Oral HPV infection in Men from the US and Latin America

03 - Epidemiology and natural history

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Background/Objectives: Oropharyngeal cancer (OPC) caused by oral human papillomavirus (HPV) is increasing globally, especially among men. Persistent HPV infection is considered the obligate precursor to HPV-OPC, though little is known regarding the duration of oral HPV infections in men. Therefore, this study aimed to evaluate clearance of oral HPV infection among prevalent and incident infections in men in the US and Latin America.

Methods: The HPV Infection in Men (HIM) study longitudinally followed 3,137 men every 6 months for up to 8 years. At each study visit men aged 18-70 completed a computer-assisted questionnaire collecting demographic and risk factor history and provided an oral gargle sample for HPV genotyping using HPV SPF PCR-DEIA-LiPA25 (DDL Diagnostics, Netherlands). Men with at least 2 oral HPV results were included in the study. Oral HPV infections were characterized as prevalent (detected at baseline) or incident (acquired throughout follow-up). Kaplan-Meier curves with log-rank test determined compared time to clearance of an oncogenic type (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) by infection type (prevalent vs incident); and by age, country, and smoking status among prevalent and incident infections separately.

Results: There were 337 men identified with an incident oncogenic oral HPV infection and 185 with an oncogenic prevalent infection. The median follow-up time was 44.8 months. The duration of infection was significantly different ($p<0.001$) between incident and prevalent oncogenic infections. Specifically, 16% of incident infections persisted more than 12 months compared to 42% of prevalent infections. Marginally significant differences were observed by age group for incident acquired infections ($p=0.051$) and significant differences by age group were observed for prevalently detected infections ($p=0.043$). Among both prevalent and incident infections, older men (age 38-81) had a longer duration of infection than mid-adult (age 28-37) and younger men (age 17-27). Although incidence of new oral HPV infection was different by country, no differences were observed for duration of either incident or prevalent infections. Similarly, no difference in oral HPV duration was observed by smoking status.

Conclusions: Our study found significant differences in duration by infection type and by age among prevalent infections. Further investigation into the factors associated with infection is needed to understand persistent oral HPV infections and who may be at highest risk of progressing to OPC.

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#4856

Sexually transmitted infections AND HPV molecular profile. A study of 336 women

40 - Public health

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Background/Objectives: The objective of this study was to investigate the potential relations of HPV co-expression with other sexually transmitted infections (STIs) and possible additional indicators that may identify increased risk for an STI during a visit to the colposcopy clinic.

Methods: Prospective study of 336 women (28.8±6.3 years, min: 18, max: 48 years) examined with liquid-based cytology (LBC) and colposcopy; their cytological samples were analyzed for HPV DNA and mRNA E6 & E7 molecular profile and the existence of additional pathogens: (Chlamydia trachomatis, Mycoplasma genitalium & hominis, Ureaplasma spp). Demographic data were also recorded.

Results: One hundred eighty individuals (53.6%) had abnormal test Papanicolaou, abnormal colposcopy was documented in 62.5%, 45.2% illustrated HPV DNA positivity and 27.4% HPV mRNA positivity. Furthermore, 40.5% of women were positive for STIs, in particular 30.4% Ureaplasma spp, 9.5% Mycoplasma spp and 0.6% Chlamydia trachomatis. STIs expression was positively related to the number of sexual partners (p=0.02), test pap outcome (p=0.04), abnormal colposcopy (OR: 1.8, 95%CI: 1.2-2.9, p=0.01), HPV DNA positivity (OR: 1.7, 95%CI: 1.1-2.6, p=0.02) and HPV mRNA E6 & E7 positivity (OR: 1.7, 95%CI: 1.1-2.8, p=0.03), notably an isolated abnormal test Pap finding was not a discriminating factor for STI prevalence (p=0.11). HPV vaccinated women were less likely to host an STI pathogen (OR: 0.4, 95%CI: 0.3-0.7, p=0.0005), but partner change during the last year was an aggravating factor (OR: 2.3, 95%CI: 1.3-4.0, p=0.005), while consistent condom use (applying a threshold of 90% use) was not correlated with STI existence (p=0.52), nor did smoking (p=0.15).

Conclusions: In this study, aspects of sexual behavior represented an important factor for a woman to host STIs (mainly Ureaplasma spp). An abnormal colposcopy as well as HPV DNA or mRNA E6 & E7 positivity can be also related to STIs and should prompt gynecologists for further investigation.

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#4789

Prevalence of human papillomavirus (HPV)-associated head and neck cancer by geography: A systematic literature review

03 - Epidemiology and natural history

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Background/Objectives: Head and neck cancers (HNCs) are the 6th most common cancer type worldwide with increasing incidence reported in many parts of the globe [1,2]. HPV attributability to HNC by anatomic site and geography is not well understood. We sought to systematically summarize the published literature on the prevalence of HPV-associated head and neck squamous cell carcinoma (HNSCC) by anatomic site and geographic region.

Methods: The systematic literature review was conducted following PRISMA guidelines. MEDLINE and EMBASE were searched for studies published in English between January 2012 and June 2022 containing type-specific HPV prevalence via polymerase chain reaction (PCR) DNA detection in histologically confirmed invasive squamous cell carcinoma (SCC) of the head and neck. Prevalence range (25th - 75th percentile) was reported in studies with DNA PCR assay-confirmed HPV positivity.

Results: A total of 352 studies were included; more from Europe (n=138) and Asia (n=132), followed by North America (n=44) and fewer from Latin America (n=21) and Africa (n=17). Total pooled sample size was the highest for oropharyngeal SCC (n=639,252), followed by oral cavity SCC (n= 484,143), and were the lowest for nasopharyngeal SCC (n=1,276). There was a wide range of reported HPV prevalence in head and neck cancers; highest in oropharyngeal SCC especially in Europe (interquartile range 16.3 - 58%) and North America (interquartile range 9 - 75.1%), and the smallest range in Africa (2.5 - 10%). For non-oropharyngeal SCC, the prevalence (Q3 range) was reported highest in APAC (oral cavity 7.7 - 36.8%, nasopharyngeal 7.9 - 31.9%, laryngeal 7.3 - 29.8%, hypopharyngeal 6.3 - 18.8%).

Conclusions: A wide range of geographic differences in HPV-associated HNCSCC by anatomic site was reported in literature likely due to heterogeneity in testing, screening, and subpopulation studied. Data were limited in Africa. More rigorous and consistent methodology in HPV detection in HNSCC would facilitate comparison and more accurate estimation of HPV attribution to HNC across regions and populations.

References: Bruni L. Human papillomavirus and related diseases in the world. 2016. Castellsagué X, Alemany L, Quer M, et al. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. J Natl Cancer Inst. 2016;108(6):djv403.

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#4686

Targeted Literature Review: Risks of HPV infection and diseases in individuals with autoimmune diseases

03 - Epidemiology and natural history

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Background/Objectives: HPV vaccination and screening programs in France are currently offered to the population according to their age. The immune status of individuals is currently not accounted for recommendations.

Methods: Literature (PubMed) was screened for English or French worldwide publications from January 2010 to December 2020 to identify and describe the burden and data gaps of HPV infections and diseases in individuals with autoimmune conditions. Focus was given to the six most prevalent autoimmune diseases in France: Hashimoto thyroiditis, Graves' disease, celiac disease, rheumatoid arthritis, type 1 diabetes mellitus and multiple sclerosis.

Results: A total of 501 records were identified following 66 PubMed database searches. In addition, 23 records were identified through other sources. Following review of all articles, 19 records were included in this targeted literature review. Only 3 out of the 6 autoimmune conditions studied had publications of interest: 1 for Celiac Disease, 12 for rheumatoid arthritis, 6 for type 1 diabetes mellitus and no records for Hashimoto thyroiditis, Graves' disease, or multiple sclerosis. This review identified populations potentially at risk for ano-genital and cervical precancerous lesions and cervical cancer, including patients with rheumatoid arthritis on biologic DMARDs (especially anti-TNF therapy) and patients with type 1 diabetes. For all the studied populations with autoimmune diseases, additional data are needed to determine with certainty their risk for HPV infection and related diseases including cancers.

Conclusions: This initial review shows data gaps that still need to be addressed and provide evidence for patient groups with trends of increased risk in HPV precancerous lesions and cancers. Additional studies are needed to confirm these trends, that could inform HPV vaccination and screening guidelines for these patients, which are currently age based.

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#4442

Geotropism and oncogenic potential of HPV infections in cohort study populations in Vojvodina, north region of Serbia

03 - Epidemiology and natural history

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Background/Objectives: Geotropism of HPV represents the heterogeneous distribution of different genotypes worldwide. According to a meta-analysis, about 12% of women are positive for HPV with normal cervical findings . Worldwide, HPV 16 is the most common genotype of HR HPV found in 60% of cervical cancer cases.HPV infection is the most common sexually transmitted disease today. This study evaluates the prevalence of HPV infection in women from Vojvodina, Serbia, according to cytological status and pathological changes of cervix, dysplasia and cancer.

Methods: The research was conducted as a retrospective study at the Oncology Institute of Vojvodina (IOV) and the Institute of Public Health of Vojvodina (IZJZV). The source of the material was the archival material of the IOV and IZJZV obtained from the medical documentation on the histopathological material from operation and cytological findings, the identified genotypes of the HPV and the age of the female patients. Cytology findings that were collected and included in the analysis were obtained by conventional Papa smear. The histopathological data that were collected resulted from the analysis of the tissue obtained by biopsy of the cervix under the control of the colposcope from the fields that showed the highest degree of abnormality or by one of the excision methods on the cervix. Genotyping of HPV DNA in cervical swab samples for all group was performed using a qualitative amplification and hybridization test. Viral DNA extraction was performed using the commercial SaMag STD DNA Extraction Kit, using the SaMag-12 Automatic Nucleic Acids Extraction System (Sacace Biotechnologies, Como, Italy) in accordance with the manufacturer's instructions. The HPV genotyping assay was performed using the EUROArray HPV test (EUROIMMUN, Luebeck, Germany) according to the manufacturer's instructions.

Results: A total of 740 women, ranging from 20 to 82 years of age, with different cytological results were enrolled. 576 samples were classified as NILM, while 164 samples belong to a group of abnormal histopathology (LSIL/HSIL/cervical cancer). Twelve HPV genotypes classified as carcinogenic to humans were detected in 252 (55%) of NILM samples, while the same genotypes were detected in 125 samples (76.2%) classified as LSIL/HSIL/cervical cancer. The most prevalent genotypes were HPV 16, 31, 53, 51, and 18 in NILM cytological status. In the samples with the abnormal histopathology, the most prevalent genotypes were HPV 16, 33, 31, and 56, while 18 and 39 were equally verified. Genotype 16 was the most prevalent in the examined sample: 18.8% in LSIL, 31.9% in HSIL, and 75% in cervical cancer samples. Infection with multiple associated genotypes of HPV is not correlated with histopathology. By comparing our female patients' histopathological diagnosis and age, we observed that older female patients had higher-grade lesions.

Conclusions: The results obtained in the cohort of female respondents in Vojvodina are correlated with other results. In cervical intraepithelial neoplasia and cervical cancer, HPV 16 has the highest oncogenic potential in our area, along with genotypes 33, 31, 18, and 56. In contrast, genotype 18 is not so prevalent in the overall prevalence in the healthy population. Genotype 16 is most often associated with pathohistological changes on the cervix. Infection with multiple associated genotypes of the HPV is not correlated with histopathology.

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#4507

Oncogenic interactions between HPV E6 and Aurora B: a novel therapeutic target?

04 - Pathogenesis

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Background/Objectives: Human papillomavirus (HPV) contributes to approximately 5% of human cancers, and accounts for 7.5% of cancer deaths in women. The high-risk HPV encoded oncoproteins, E6 and E7, can activate DNA damage response, induce a global increase in expression of cyclin-dependent protein kinases (CDKs), and increase genome instability. Recent reports showed that members of the Aurora kinase family of serine/threonine kinases are involved in HPV-mediated carcinogenesis. The objectives of this study were examine the physical association between E6 and Aurora B (AurB), and to delineate the consequences of AurB-E6 complex on key oncogenic pathways.

Methods: A series of in vitro and cell-based assays were performed to investigate the physical association between E6 and AurB, and the effects of AurB-E6 complex formation on histone activation, human telomerase reverse transcriptase (hTERT) expression and Ras/MEK/ERK signaling axis.

Results: We showed that AurB activity was elevated in HPV-positive cells, and this correlated positively with E6 expression as demonstrated by overexpression and depletion experiments. E6 interacted directly with AurB in the nucleus or in mitotic cells. Aurora kinase B interacted directly with C-terminus of HPVE6, independent of E6-PBM. We found that a previously unidentified region of E6, upstream of C-terminal E6-PBM, was important for AurB-E6 complex formation. Of note, AurB co-immunoprecipitated with HPVE6, but not HPVE7. AurB-E6 complex led to reduced AurB kinase activity. However, AurB-E6 complex activated histone H3, elevated the Ras/MEK/ERK signalling axis, and increased hTERT protein level and its telomerase activity. Inhibition of AurB affected survival, proliferation and tumour formation of HPV-positive cells.

Conclusions: In summary, this study dissected the molecular mechanism on how E6 recruits AurB to induce cell immortalization and proliferation leading to the eventual cancer development. Thus, setting a new horizon for designing novel targeted therapies tailored for HPV-associated cancers.

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#4728

Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis

06 - HPV prophylactic vaccines

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Background/Objectives: The efficacy of human papillomavirus (HPV) vaccination on the risk of recurrent diseases related to HPV infection in individuals undergoing local surgical treatment constitutes a matter of debate.

Methods: In this study we screened data sources for studies reporting on the risk of HPV infection and recurrence of disease related to HPV infection after local surgical treatment of preinvasive genital disease in individuals who were vaccinated. Independent and in duplicate data extraction and quality assessment were performed. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was implemented for the primary outcome (recurrence of cervical intraepithelial neoplasia grade 2 or higher (CIN2+)). Pooled risk ratios and 95% confidence intervals were calculated with a random effects meta-analysis model.

Results: 18 studies reported data from a non-vaccinated group and were included in the meta-analyses. The risk of recurrence of CIN2+ was reduced in individuals who were vaccinated compared with those who were not vaccinated (11 studies, 19 909 participants; risk ratio 0.43, 95% confidence interval 0.30 to 0.60; $I2=58\%$, $\tau2=0.14$). The effect estimate was even stronger when the risk of recurrence of CIN2+ was assessed for disease related to HPV subtypes HPV16 or HPV18 (six studies, 1879 participants; risk ratio 0.26, 95% confidence interval 0.16 to 0.43; $I2=0\%$, $\tau2=0$). Confidence in the meta-analysis for CIN2+ overall and CIN2+ related to HPV16 or HPV18, assessed by GRADE, ranged from very low to moderate, probably because of publication bias and inconsistency in the studies included in the meta-analysis.

Conclusions: HPV vaccination might reduce the risk of recurrence of CIN, in particular when related to HPV16 or HPV18, in women treated with local excision. Large scale, high quality randomised controlled trials are required to establish the level of effectiveness and cost of HPV vaccination in women undergoing treatment for diseases related to HPV infection.

References: Kechagias, K.S.; Kalliala, I.; Bowden, S.J.; Athanasiou, A.; Paraskevaidi, M.; Paraskevaidis, E.; Dillner, J.; Nieminen, P.; Strander, B.; Sasieni, P.; et al. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: Systematic review and meta-analysis. BMJ 2022, 378, e070135.

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#4670

Impact of Catch-up HPV Vaccination

06 - HPV prophylactic vaccines

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Background/Objectives: Each year in France, more than 3000 new cases of cervical cancers are recorded. The vaccinal cover stays insufficient since less than 41% of the French population is vaccinated. Therefore French studies about vaccine efficacy and especially about the catch-up vaccine (administered after 15 years old) are needed. HPVAC2 is an analytic study designed to learn the impact of the catch-up HPV vaccination. Indeed, 347 women from 25 years old and born after 1984 were included when they came to the Brest CHU to do their regular cervical smear. At this time, they had to fill out a survey for us to know their vaccinal status. The aim of the study is to prove the efficacy of the catch up vaccination by analyzing the cervical smears results and by comparing the vaccinated group with the not-vaccinated group.

Methods: Primary outcome: Analyses of smear tests and HPV-tests to study the effectiveness of the catch-up HPV vaccination (given between 15 and 19 years old). Secondary outcomes: Study the effectiveness of HPV vaccination, not regarding of the realization period. Compare the effectiveness of HPV vaccination administered before and after 15 years old. Analyze the impact of the known cervical cancer risk factors on the smear tests and HPV tests results. Study design: HPVAC2 is a case-control, non-interventional, analytic and monocentric study. Patients have been included from the end of May 2021 to the end of June 2022 (time frame: 13 months). Analyses were done in groups (vaccinated vs non vaccinated) and adjusted on covariates.

Results: There is a global significant protection given by the vaccine on the smear tests and HPV tests results (odds ratio=0,27 ; p=0,005). Subgroups analyses show a significant reduction of pathologic results by the vaccine given before 15 years old (primo-vaccination) (odds ratio=0,34 ; p=0,002). However, we have not been able to demonstrate a significant efficacy of the vaccine administered after 15 years old (odds ratio=0,93 ; p=0,89). Only smoking and early sexual life start (in the complementary analysis) were proved as risk factors.

Conclusions: This study reinforces the importance of the anti-HPV vaccination by proving its protection. More work needs to be done to study the catch up efficacy, although it seems that the sooner the vaccine is done, the better is the cover. The major limit of HPVAC2 is the number of missing data in the form patients had to fill out. Nevertheless, the multivariate model created by adjusting on covariates strengthens our study. More research on the subject is needed to improve the French vaccination adhesion and maybe to widen the indications.

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#4907

The effectiveness of the combined treatment of potassium-titanyl phosphorous (KTP) laser resection and adjuvant human papillomavirus (HPV) vaccination for laryngeal papillomatosis: a preliminary study

07 - HPV therapeutic vaccines

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Background/Objectives: Laryngeal papillomatosis is a rare but challenging disease. It is caused by human papillomavirus(HPV) 6 and 11 infection that represents a high rate of multisite recurrence and burden on patient quality of life. In this study, we report a case series treated with 532 nm potassium-titanyl phosphate (KTP) laser surgery and an HPV 9-valent vaccination for laryngeal papillomatosis.

Methods: We retrospectively analyzed the medical records of eight newly diagnosed laryngeal papilloma patients from 2018 to 2020. The patients were all treated with the KTP laser, followed by being inoculated three times with Gardasil-9®. We analyzed the recurrence and the result of the voice analysis after this combination treatment.

Results: All eight patients confirmed HPV subtype 6. The mean follow-up period of the patients was 24.5 months. Two patients (25%) developed recurrence after treatment. The total number of operations was 15, and the average number of operations per month was 0.08. In voice analysis before and after the combination treatment, the voice handicap index (VHI-10) improved from 13.5±7.6 to 5.5±12.4(p=0.041), and the GRBAS score improved from 6.3±2.7 to 3.4±1.5 (p = 0.038).

Conclusions: This is the first study for the treatment of laryngeal papillomatosis using both KTP laser surgery and HPV vaccination. The combined treatment may be useful in the treatment of laryngeal papillomatosis. Despite this, further non-randomized multicenter study is needed to confirm the efficacy of the combination treatment for laryngeal papillomatosis.

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#4975

Suppression of inhibitory receptors of CD8 T cell and expression of chemokine receptor eradicated effectively cervical cancer in mouse.

07 - HPV therapeutic vaccines

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Background/Objectives: Activation of exhausted CD8 T cell and migration of immune cells into tumor site is an important for overcoming resistance to cancer therapy. We evaluated the role of suppression of inhibitory receptors and chemokine axis in cervical cancer bearing mouse.

Methods: C57BL/6 mice were categorized into four groups according to treatment modality. Mice were challenged with 1×105 TC-1 cells on cervix. HPV DNA therapeutic vaccine was injected intramuscularly and intratumoral injection of GMCSF was performed. The mice were harvested on day 21 and immune cells were investigated by flow cytometry. We checked the expression of inhibitory receptors of CD8 T cells, including PD1, TIM3 and LAG3. Chemokine axis such as CXCL9, CXCL10, and CXCR3 were evaluated to know migration mechanism.

Results: Combination of HPV DNA vaccine and GMCSF resulted in significantly lower expression of TIM3 inhibitory receptors of CD8+ T cells in tumor ($p<0.05$). However, expression level of PD1 and LAG3 was not changed after combination therapy. They significantly induced accumulation of tumor specific CD8 T cell in tumor site and increased expression of CXCR3 on tumor infiltration CD8 T cell ($p<0.05$). CXCL9, chemokine, was overexpressed in cervical cancer after combination therapy ($p<0.05$). However, expression level of CXCL10 was not changed after combination therapy. Finally, mice treated with combination therapy survived significantly longer than other groups with single therapy ($p<0.05$).

Conclusions: In conclusion, we overcame T cell exhaustion and identified chemokine axis during migration of CD8 T cell into cervical cancer using HPV DNA vaccine and GMCSF. This mechanism can be ideal target for future immunotherapy.

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#4861

Prevention Of HPV Reinfection With HPV Vaccination After Laser Vaporisation And Conization In Reproductive Age Patients With HSIL

07 - HPV therapeutic vaccines

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Background/Objectives: Background and aims: Prevention of Human Papilloma Virus (HPV) reinfection by "Gardasil" after surgical treatment of patients with high grade intraepithelial lesion HSIL-CIN2 and HPV infection.

Methods: Methods: For our preliminary study we investigated 145 patients with HSIL-CIN 2 (Pap smear,colposcopy, biopsy, immunohistochemistry P16+).

Results: Results: All investigated patients (n=145) with HSIL-CIN 2 were treated by Co2 Laser conisation and vaporisation. They were suggested vaccination by "Gardasil". Main control group included 53 patients who agreed vaccination. They were treated by "Gardasil" after surgical procedure and before sexual activity. Study group included 92 unvaccinated patients. There were made control PAP smear, colposcopy and PCR detection of HPV (Type - 6,11, 16, 18, 31) infection after surgical treatment with 3months intervals during one year. HPV induced lesion was statistically significant at 6, 9 and 12 months ($p<0.05$).

Conclusions: Conclusions: Based on our preliminary data we can supposed, that vaccination by "Gardasil" after laser surgery of intraepithelial lesion may prevent reinfection in patients with HPV.

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HSIL and Gardasil

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#4636

The impact of PIK3CA mutations on HPVE7 expression, PD-L1 (CD274) expression in HPV16 cervical SCC

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Cervical cancer (CC) is an important HPV-driven tumor and is highly recognized by the immune system. Somatic PIK3CA (p110a) mutations are frequent in CC and HPV oncoproteins are targets of immunotherapies. Although immunotherapy targeting T cell checkpoints such as PD-L1 show promising results, durability is limited. The association between PIK3CA mutations and PD-L1 (CD274) expression in CC are unknown

Methods: Analysis of TCGA-CESC data sets; Culture cervical cancer cell lines and treated with specific inhibitor; Western Blotting; Cell proliferation assay; Nanopore RNA sequence; T cell killing assay

Results: To explore the effect of mutations on PD-L1, we used Apelisib/BYL719 (a selective inhibitor of PIK3CA mutation). Analysis of TCGA-CESC showed that PD-L1 and APOBEC3A expressionare significantly higher in HPV16 SCC patients with PIK3CA mutations. PD-L1 protein expression are elevate in PIK3CA mutated CaSki cells (HPV16, PIK3CA E545K) than cell lines with WT PIK3CA SiHa (HPV16, PIK3CA WT). BYL719 significantly inhibits the protein levels of PD-L1 as well as YAP, EGFR, Integrin, IRF1, HPV16 E7 in CaSki, SNU17 (HPV16, PIK3CA E545Q) and ME180 (HPV68 PIK3CA E545K), but not in SiHa. BYL719 also dramatically inhibits the proliferation of PIK3CA mutated, but not WT cell lines. RNA sequencing results shows CaSki cells treated with BYL719 have significantly lower levels of HPV16 oncogene expression and host immune-system related genes including HLA-A, B2M, IRF1, NFkB, APOBEC familyand cell cycle related genes. Treatment of HPV positive PIK3CA mutant cell lines with tumor antigen-targeted CD8+ T cells (NEXI003, NexImmune) inhibited/killed HPV positive PIK3CA mutant cells in an effector : target cell ratio dependent manner. Combination treatment of these effector T cell with BYL719 showed equivalent or greater inhibition/killing of CaSki cells than either treatment alone.

Conclusions: Molecular inhibitors targeting PIK3CA, in combination with PD1/PD-L1 inhibitor may improve the outcome of advanced HPV16 positive cancers.

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#5582

HPV- negative premalignant and malignant changes in the cervix: myth or reality

09 - HPV testing

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Background/Objectives: The percentage of HPV- negative cancers cited in literature varies from year to year. With the development of new technological possibilities (DNA sequencing), immunohistochemistry and newer generation tests, the number of false-negative HPV cancers is decreasing. A larger meta-analysis reported a steady decline in the percentage of HPV-negative cancers. In the period from 1990 to 1999, it was 14%, in the next 10 years, this percentage decreased to 12%, and by 2010 it would fall to 7%. 1. What remains unknown is the percentage of true cancers that are HPV negative and does do not detect HPV proving that cancer is not caused by HPV infection?

Methods: Possible reasons that explain why cervical cancer can be HPV negative are as follows: 1. errors in HPV testing and 2. cervical cancer which loses HPV expression after initial infection 3. cancer caused by the benign HPV virus 4. Errors in the histological interpretation of the findings 5. metastatic carcinomas of the cervix 6. Histological types of HPV- negative adenocarcinoma7. cervical cancer independent of HPV infection The largest difference in the percentage of HPV negativity was related to the histological type of cancer. 75-90% of cervical cancers are of the squamous histological type, while the remaining 10-25% qre of theadenosquamous and adenosquamoustypes, as well as rare forms of cancer including: melanoma, lymphoma, sarcoma and neuroendocrine tumor. 2.

Results: The results of our research shown in table no. 1 show that the percentage of HPV-negative cancers was approximately 10%. In relation to the histological type, the percentage of HPV-negative patients was higher in adenocarcinomas than in squamous adenocarcinomas (28.6:8%). Table 1. HPV test results for adenocarcinoma and other squamous lesions PH findings HPV positive-negative p HPV- HPV+ In total AC 6 15 21 0.004 28.60% 71.40% 100.00% rest 12 138 150 8.00% 92.00% 100.00% In total 18 153 171 The HPV- negative histological subtypes of adenocarcinoma are serous, clear cell, mesonephric, endometrioid from the upper part of the endocervix and lower uterus, and gastric. On the other hand, adenocarcinomas can also be falsely HPV negative due to the low viral load of the fragile, thin, single-row endocervicaladenoepithelium. Table 2 shows that the percentage of false-negative cytological findings in adenochanges was 85.7 Table No. 2. Cytological findings in adenocarcinoma (AC) and other squamous lesions PH findings cytological findings PH findings NILM ASCUS, LSIL HSIL, IC In total AC 18 3 0 21 < 0.001 85.70% 14.30% 0.00% 100.00% rest 21 69 69 159 13.20% 43.40% 43.40% 100.00% In total 39 72 69 180

Conclusions: However, HPV testing significantly aids in the detection of adenocarcinoma, because the cytological PAP test shows a higher percentage of false negative results in relation to the HPV test. HPV negative cervical carcinomas should be considered by the clinician when it comes to cervical cancer screening, but this should certainly not reduce the importance of HPV testing and vaccination.

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#5427

Association between common vaginal and HPV infections and results of cytology test in the Macedonian women

09 - HPV testing

Background/Objectives: Based on epidemiological and laboratory studies, human papillomavirus (HPV) is considered a primary cause of uterine cervical cancers. The global prevalence of HPV in cervical cancers is over 99% which actually means that all cervical cancers have HPV infection. There also have been several studies regarding the role of genital co-infections in the development of cervical intraepithelial lesions (CIN) and cervical cancer in HPV infected woman. It is the biological susceptibility for HPV infection and the immunological ability for resolving this infection that can be influenced and altered by the genital co-infections by a manner of breaking the inborn protective mechanisms against HPV infection. The aim of this study was to examine the association between the human papilloma virus infection and genital co-infections with cervical intraepithelial neoplasia / cervical carcinoma, and the correlation between HPV infections and other genital co- infections.

Methods: The number of patients who underwent liquid based cervical cytology and histology verifications during the period of 2013 to 2016 was 9579. ASCUS, CIN I, CIN II , CIN III, CIS or cervical carcinoma were the abnormal results from cervical PAP smear. Histological verification was done only in the cases with cervical carcinoma or adenocarcinoma. The number of positive patients was 2309 , and were compared to the 5803 patients in the control group with normal cytology on PAP smear. Both groups were tested for seven types of genital co-infections.

Results: The overall rate of HPV infection was 27.6 %. HPV infection was most common in patients with CIS, cervical carcinoma and adenocarcinoma (94,4 %, 98,0 % and 100 % respectively). The most common genotype was HPV typ 16 in 30.1 % of all patients as self sufficient or in combination with other type. The most common genital co-infections were Ureaplasma parvum (UP) Ureaplasma urealyticum (UU) and Chlamidia trachomatis (CT) an there was statistically significant association between HPV infections with UP, MH and CT infections.

Conclusions: There is strong correlation between HPV infection and cervical carcinomas. Associations between HPV infection with Ureaplasma parvum, Mycoplasma hominis and Chlamydia trachomatis can in part be explained as a result of the co-infection, taking in consideration that they share the same route of transmission. Infection with sexually transmitted pathogens is associated with separate cytological diagnoses ASCUS, CIN I, CIN II, but not with CIN III, CIS, invasive cervical cancer.

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#5188

Evaluation of the HPV Selfy Extended assay for HPV genotyping of anal cytological specimens

09 - HPV testing

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Background/Objectives: The large majority of anal carcinomas are caused by high-risk HPVs, with an overall prevalence of 98% in HIV-infected men and a dominant role for HPV16 (67-82%). Although populations at higher risk for anal cancer, such as HIV-infected men who have sex with men (MSM), could benefit from preventive strategies, anal cancer screening is currently based on expert opinion and consensus national/international guidelines are lacking. The clinical value of testing and genotyping anal samples of at-risk individuals is still debated, thus further research in this regard is needed. We aimed to evaluate the performance on anal samples of the HPV Selfy Extended, a CE IVD assay that can detect individually 30 HPV genotypes exploiting a Real Time PCR followed by post-PCR melting curve analysis.

Methods: A retrospective study was conducted on DNA specimens purified from anal cytological samples and stored at -20°C. Anal cells from HIV-infected and HIV-uninfected MSM were collected using a Dacron swab and dispersed in PreservCyt. Nucleic acid extraction was performed using the Amplilute Liquid Media Extraction kit. Samples with a valid result with the Linear Array HPV Genotyping test (LA) were selected for the study. DNA samples were then tested with the HPV Selfy Extended. Overall and type-specific concordance as well as Cohen's kappa were estimated, limiting the analysis to the 28 HPV types detectable by both assays.

Results: Eighty-five anal samples that had a valid result with both tests (i.e., positivity for the beta-globin internal control) were included in the analysis. Of these, 77 (90.6%) were positive and 8 negative (9.4%) both by HPV Selfy and LA. Concordance between the tests was 100% for HPV status. Among the 77 HPV-positive samples, a multiple infection was detected in 74 (96.1%; 2 to 9 HPV types) and 75 cases (97.4%; 2 to 9 HPV types, except for two cases with 12 and 13 HPV types, respectively) by HPV Selfy and LA, respectively. HPV Selfy detected 339 infections, of which 186 by high-risk (54.9%), 44 by possibly high-risk (13.0%), and 109 by low-risk types (32.2%). Instead, LA detected 353 infections, of which 207 by high-risk (58.6%), 54 by possibly high-risk viruses (15.3%), and 92 by low-risk types (26.1%). Overall, type-specific concordance between the tests was 90.0% (Cohen's K =0.77). Regarding the individual types, concordance ranged from 81.2% to 98.8%. The most frequently detected HPV type was HPV16 with both assays (37/85, 43.5% with HPV Selfy, and 35/85, 41.2% with LA), with a concordance of 81.2% (Cohen's K = 0.51).

Conclusions: When employed on anal samples, a 100% concordance between HPV Selfy Extended and LA in terms of HPV status, and a good agreement in terms of genotyping, were observed. HPV Selfy Extended assay combines a simple processing protocol, requires limited equipment, and is less labor-intensive with respect to other genotyping assays. In addition, PCR reaction is completed in less than one hour. HPV Selfy, which has been clinically validated for primary cervical cancer screening, is worth further investigation as a tool for HPV detection in anal cytological samples.

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#4997

Impact of cut off values for BD onclarity HPV assay in clinical testing

09 - HPV testing

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Background/Objectives: BD Onclarity HPVTM assay is validated for primary screening in Europe according to international guidelines. The test is indicated for triage of ASCUS cytology as well, but is not validated for diagnostic testing, i.e. in women with symptoms, in follow-up after previous positive tests and in follow-up after conization for CIN2+. In the Onclarity assay six HPV genotypes are detected individually (16,18,31,45,51 and 52) and eight genotypes in three bulks (33/58, 56/59/66 and 35/39/68). The PCR cycle threshold (CT) for test positivity is set higher for HPV16 (CT 38,3) than for the other genotypes (CT 34,2), but all CT values up to CT 40 are recorded and readily available. We wanted to investigate the impact of these threshold values when BD Onclarity is used in diagnostic testing.

Methods: Diagnostic cervix samples with CT value between 34,3-38,3 (other HPV types than HPV16) in their Onclarity HPV test results were registered and classified as having grey zone values. Among those, samples with CT values ≤36 were classified as having near-cut off values. Exclusion criteria was HPV positivity for another HPV type. Exclusion criteria was not applied to grey zone HPV18 samples, because an HPV18 positive test result has implication for the follow-up recommendation according to the Norwegian guidelines. Follow-up samples, either cytology, HPV test or histology were registered for up to 12 months following the index grey zone HPV test result. 95 samples were co-tested with Cobas 4800 HPV assay, also validated only for primary screening and triage of women with ASCUS. For several years, Cobas 4800 HPV has also been used for diagnostic testing in Norway, and serve as basis for recommendations of test intervals in women in different clinical settings.

Results: In total 162 women were included in the study; 90,1 % had a concurrent normal cytology, 8,6% ASCUS, 0,6% LSIL and 0,6% HSIL. Follow-up samples were available for 118 women. 32% (38/118) had persistent infection, where 14%(17/118) were positive for the same grey zone type as in the index sample, while 18%(21/118) were still grey zone positive. HPV persistence rate varied according to genotype. In particular 59% (10/17) of women with HPV 18 grey zone index sample, were positive or still grey zone for that genotype in follow-up samples. Histology results were available in 34 women. Normal histology was present in 79%, CIN1 in 12% and CIN2-3 in 9%. Among samples co-tested with Cobas 4800, 37 out of 95 cases had near-cut-off CT values with BD Onclarity. Among those, 73%(27/37) revealed a positive Cobas test. For HPV45, 88%(7/8) were positive in both tests regardless of grey-zone CT value.

Conclusions: A majority of women with a HPV test taken in clinical setting and with grey zone values near cut off CT values would receive a closer follow-up if tested with the Cobas 4800 assay compared to BD Onclarity, when cut off CT values from the manufacturer are followed. HPV persistence in follow-up samples was more often seen for HPV18, where over 50% of the samples were positive or still grey-zone positive for that genotype. The clinical impact of detecting these infections in women who are referred in a clinical setting remains to be determined and longer follow-up period is needed.

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#4867

Pre-vaccination prevalence of high-risk human papillomaviruses (HR-HPV) in the Montenegro prior to national HPV immunisation programme: baseline for monitoring the effects of immunisation

09 - HPV testing

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Background/Objectives: To determine the pre-vaccination prevalence and distribution of the 14 most common HR-HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 by age in Montenegrin women, in order to be able to predict and monitor the impact of HPV immunization in Montenegro (9-valent human papillomavirus, 9vHPV, Gardasil 9®, Merck Sharp & Dohme), which started on September 26th, 2022.9vHPV is a non-infectious, virus-like particle (VLP) vaccine. Vaccine contains HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 VLPs. 9vHPV was the first time approved by the Food and Drug Administration (FDA) on December 10, 2014, for use in females aged 9 through 26 years and males aged 9 through 15 years. The European Commission granted a marketing authorization valid throughout the European Union for Gardasil 9 on 10 June 2015. In Montenegro, HPV vaccination is primarily recommended for the girls aged 9, with plan for catch up vaccination for girls aged 10-14 during next several years.

Methods: Cervical smears were collected from 8 048 women, aged 13-80 years, attending the outpatient department at the Institute of Public Health of Montenegro, during the period from September 2019 till the September 2022. Cervical samples were tested for HPV L1 region by RealTime High Risk HPV assay (Abbott, USA). Assay can differentiate high risk HPV genotypes 16 and 18, and remaining 12 HR-HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are reported as Other HR HPV.

Results: The overall prevalence of 14 HR-HPV genotypes was 24.09%, with the dominance of Other HR HPV genotypes (67%) over the genotype 16 (16,45%). The presence of HPV genotype 18 was found in 4,58% of all HPV positive cases. Multiple genotype HPV infection was found in 11.96% of the HPV infected samples. The prevalence of the HPV multiple infection was highest at the age group 25-34 years and it was reduced at older ages. The most common combination was of HPV genotype 16 with Other HR HPV genotype (8,00%). In general, prevalence of HR-HPV infection was highest in the age group 25 to 34 years (44,45%). It decreased progressively with increase of age, up to 2,84% in the age group 55 to 64 years. After that age, there were less than 1% HPV positive cases. In our study, the youngest age group (<25 years) appears to had infection rates of 15.06%.

Conclusions: Out of all HPV positive samples, our results show that 2/3 of cases were positive for some of the 12 HR HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Establishing this baseline distribution will help to monitor the early impact of vaccination (9-valent human papillomavirus, 9vHPV) and to monitor possible changes in genotype-specific HPV distribution after vaccination has been introduced.

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#4821

High-grade cervical lesions at start of screening age in Danish women HPV-vaccinated as girls

09 - HPV testing

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Background/Objectives: In Denmark, three-yearly cytology screening starts at age 23, and follow-up depends on cytology outcome. HPV-vaccination began in 2008. Optimal screening strategy for women HPV-vaccinated as girls is not straightforward, as these women have lower cervical cancer risk than previous generations. Our study (Trial 23) provides knowledge on the first screening outcome in women HPV-vaccinated as girls.

Methods: Trial23 is a method study embedded in the nationwide screening program. It includes women born in 1994, living in half of Denmark, and first time invited to screening. We recruited women screened from 1 February 2017-2 July 2021. Following national guidelines, all screened women had routine cytology and clinical management was based on this test only. For a randomly selected 50% of women, their samples were also HPV-tested. Follow-up diagnosis was most severe histology/cytology outcome between baseline screening date and 795 days later. Data were retrieved from the Danish Pathology Register.

Results: In total, 11,892 women were screened. Vaccination coverage was 92%. Among the 6021 HPV-tested women, 35% were HPV-positive, of which 16 and/or 18 accounted for only 0.8%. In women cytology positive/HPV-positive (Cyt+/HPV+), 610 women had been followed up, and 138 had cervical intraepithelial neoplasia (CIN)2+ diagnosed; in women Cyt+/HPV- numbers were 76 and 5, and in women Cyt-/HPV+ 182 and 8. For double positive women, Cyt+/HPV+, 4.4 women were followed up per detected CIN2+; for Cyt+/HPV- it was 15.2; and for Cyt-/HPV+ it was 22.8. To find one CIN3+ 8.6 women with Cyt+/HPV+ were followed up.

Conclusions: In Danish women, HPV-vaccinated as girls and Cyt+/HPV+ at first screen around age 23, a follow-up of four women were needed to detect one CIN2+ case and nine women for one CIN3+ case. Numbers were considerably higher for women with Cyt+/HPV- and Cyt-/HPV+, suggesting that immediate follow-up should be focussed on double positive women.

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#5789

Comparison of Allplex HPV Detection using cervical specimens, the fast and comprehensive assays suitable for HPV screening and genotyping

09 - HPV testing

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Background/Objectives: Human papillomavirus (HPV) is a well-identified factor that influences incidence and progression of cervical cancer. As many studies reported the high sensitivity and specificity of HPV testing, several countries had started to implement HPV testing into the national screening program. Taking one step forward, several studies have shown the correlation of HPV Ct values with the severity of cervical lesions. In the line with the trends, the novel HPV testing assay, AllplexTM HPV HR and HPV28 Detection, has been launched, which specifically and simultaneously detects individual HPV genotypes and provides each of Ct values in cervical and self-collected vaginal specimens. Here, we aim to evaluate the clinical performance of AllplexTM HPV HR and HPV28 Detection using cervical specimens.

Methods: To evaluate AllplexTM HPV HR Detection, NIMBUS was used to extract DNA from 816 cervical specimens. In the case of AllplexTM HPV28 Detection, DNA was isolated from 536 cervical specimens with STARlet instrument. Each of the manufacturer's instructions was followed in the cases of CE-approved assays.

Results: Among 816 cervical specimens composed of 413 CIN 2+ and 403 <CIN 2, AllplexTM HPV HR Detection displayed relative sensitivity of 98.74% and relative specificity of 98.45% by comparing to a CE-approved assay. Positive percent agreement (PPA), negative percent agreement (NPA) and overall percent agreement (OPA) were 98.14%, 95.98% and 97.55%, respectively. In the comparison of AllplexTM HPV28 Detection, PPA, NPA and OPA were 91.67%, 96.73% and 95.71%, respectively, compared to the other CE-approved assay in 536 cervical specimens.

Conclusions: AllplexTM HPV HR and HPV28 Detection exhibited comparable performance in cervical specimens compared to other CE-approved assays. Especially, AllplexTM HPV HR Detection would be the highly useful HPV testing for cervical cancer screening as providing individual high-risk HPV genotypes and may help patient management through each of obtained HPV Ct values.

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#5301

14 HR HPV detection: the Lazio experience in the national HPV-based cervical cancer screening in Italy

10 - HPV screening

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Background/Objectives: In the Lazio Region the national cervical cancer screening program for women from 30 to 64 years old is based on the detection of 14 HR HPV genotypes. The screening interval is 5 years. Our centralized laboratory, in Rome near the Colosseum, is one of two selected for HPV testing in our Region. Identification of HPV genotypes is important not only for epidemiology purposes but also because the persistence of an infection is a necessary condition for the development of cervical cancer. Furthermore, HR HPV genotypes have a different risk of progression. The purpose of our study was to analyze the prevalence of the 14 HR HPV genotypes in our laboratory, during six months (April to November 2022).

Methods: We evaluated 30,445 samples received in our laboratory from April to November 2022. The samples were analyzed using the Anyplex TM II HPV HR Detection test by Seegene (Arrow), a Real time PCR method based on DPOTM technology (Dual Priming Oligonucleotides) and TOCETM (Tagging Oligonucleotide Cleavage and Extension) which identifies the 14 HR HPV: 16, 18, 31,33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 (343 sessions processed and reported from April 28th to November 18th, 2022). The data were evaluated using the SG STATS platform for statistical analysis (Seegene, Arrow).

Results: We had 4,244 samples that tested positive for HR HPV (13,9%). The total positive samples for only one genotype were 3,290 (77.5%), those with co-infections (from 2 to 5 genotypes) were 954 (22.5%). Total prevalences (single infection and co-infections) were: HPV 16 755 cases 13.8%, HPV 31 704 12.9%, HPV 68 580 10.6%, HPV 66 436 8.0%, HPV 52 413 7.5%, HPV 58 411 7.5%, HPV 51 400 7.3%, HPV 56 366 6.7%, HPV 39 293 5.3%, HPV 59 260 4.8%, HPV 45 231 4.2%, HPV 33 230 4.2%, HPV 18 222 4.0%, HPV 35 173 3.2%. The inadequate cases were 23 (0,0755%) due to technical pitfalls and 28 (0,0919%) due to poor cellularity. After repetition, we reported 18 inadequate cases (0.0591%) due to poor sample cellularity.

Conclusions: Our results indicate that HPV 16 and 31 are the most prevalent in the Lazio Region followed by HPV 68, 66, 52, 58, 51 and 56 infections. These results are useful both for the treatment and prognosis of the patients and for the epidemiology of the infection considering however that the scenario could change with the enrollment in the screening of vaccinated girls. The possibility to detect 14 HR HPV single genotypes allows a better risk stratification and identification of multiple HPV genotypes infections.

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#5234

Cervical intraepithelial neoplasia in non-16/18 high-risk HPV positive/cytology negative women: An alternative approach in poor resource areas

10 - HPV screening

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Background/Objectives: Since the specific prevalence and carcinogenesis of non-16/18 high-risk (hr) Human Papillomavirus (HPV) is not fully understood, we designed a study with aim of evaluating the risk of high-grade cervical intraepithelial neoplasia (CIN) in non-16/18 hr-HPV positive/cytology negative cases and assessing the distribution of non-16/18 hr-HPV subtypes.

Methods: This cross-sectional study was conducted on 138 non-16/18 hr-HPV positive/cytology negative women, who were referred to the gynecologic oncology clinic of Yas hospital, affiliated with Tehran University of Medical Sciences, January 2021 to 2022. HPV Direct Flow CHIP (Master Diagnóstica, Granada, Spain) is used for sensitive HPV detection and genotyping and is CE-IVD marked in compliance with European Union diagnostic medical device manufacturing standards. Cervical cytology evaluation was performed by liquid-based cytology (LBC). One specific qualified gynecologic oncologist with over 15 years of experience in colposcopy did all of the colposcopic exams and biopsies. Cervical biopsy was done if indicated based on colposcopic examination with acetic acid 3% application. To further validate the results, all of the cervical cytology and biopsies were reevaluated by one specific expert gynecologic pathologist.

Results: Of 138 patients included in this study, 63 cases underwent biopsy as indicated during colposcopy among which 34 had normal results. In the remaining 29 cases, 25 had insignificant findings such as CIN1 (15 cases), flat condyloma (5 cases), chronic cervicitis with features of HPV effect (3 cases), and basal cell abnormalities of uncertain significance (2 cases). Four cases were high-grade CIN. The incidence of CIN2 and CIN3 was 1.4% and 1.4%, respectively. In 105 cases (76.1%), a single type of HPV was detected, while in 33 (23.9%) women, more than one type of HPV was reported. Among the detected types of HPV, HPV 31 was the most frequent type (Figure. 1).

Conclusions: Our study showed that the risk of CIN among non-16/18 hr-HPV positive/cytology negative cases is noticeably low. Based on ASCCP guidelines return testing at 1 year without immediate colposcopy seems sufficient; however, due to many reasons listed below, it may be more reasonable & practical to choose colposcopy over a 1-year follow-up when confronted with non-16/18 hr-HPV positive/cytology negative women at least in resource-poor, low-income countries such as ours: First, we do not have a national vaccination program and insurance companies which support HPV vaccination in our country so there is no protection against HPV infection in this regard. Secondly, due to the lack of a national screening program and a systematic recall in our country, the rate of follow-up misses is very high. Thirdly, the colposcopic examination is much cheaper than the HPV test or co-test nearly one-seventh in price, which makes colposcopy a more accessible option. Fourthly, the previous history of HPV tests in many patients is unknown which is highly worrisome for most patients and 1-year follow-up is not reassuring for this group of patients. Lastly, despite the low rate of cervical cancer in Iran (0.0025%), its mortality is high due to its diagnosis at the advanced stages, so even missing one case can lead to high-cost expenditures and even loss of a young woman of low socioeconomic status probably in her child-bearing age with many little children to nurture, and in this way, great damage to society will be caused both materially and spiritually.

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#5049

Performance Evaluation of the cobas® 5800 System and Comparison to the cobas® 6800/8800 Systems for Clinical Validation of cobas® HPV

10 - HPV screening

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Background/Objectives: The cobas® 5800 System ("cobas 5800")is a new PCR-based nucleic acid testing system designed to satisfy the needs of low to mid-throughput laboratories.1 The cobas HPV Test ("cobas HPV") is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) in patient specimens and has been previously validated by Meijer criteria on the cobas® 4800, and cobas® 6800/8800 systems, which share similar features and specifications as cobas® 5800. 2, 3, 4, 5

Methods: For evaluating sensitivity and specificity, samples from CIN2+ cases and <CIN2 non-cases were selected from the IMPACT trial. IMPACT (IMproved Primary screening And Colposcopy Triage) was a multicenter, prospective study conducted to evaluate the performance of cobas® HPV on the cobas® 6800/8800 Systems, as a triage test to stratify women with ASC-US Pap cytology results for colposcopy, as an adjunctive test to cervical cytology to guide management decisions in women with NILM Pap cytology, and as a first-line primary test for cervical cancer screening. Outcomes were histologically confirmed by a team of central pathology reviewers. 2,571 samples were selected from IMPACT. Cervical specimens collected in PreservCyt® Solution comprising 171 histologically confirmed ≥CIN2 cases including 60 ≥CIN3 cases, as well as 2,400 histologically confirmed <CIN2 cases were used to assess the assay performance. These cervical specimens in PreservCyt® were randomly and evenly divided among all cobas Systems. Reproducibility was assessed using a co-formulated HPV panel (HPV 16 and HPV 18) comprising 2 concentrations per target plus a blank. Reproducibility was assessed across 3 laboratory sites, over 5 days, 2 runs per day per instrument, 3 replicates per panel per run, on both cobas® 5800 and cobas® 6800/8800 Systems.

Results: The ratio of the sensitivities of cobas® HPV on the cobas® 5800 System and cobas® 6800/8800 Systems for the detection of ≥CIN2 was 1 with the lower limit of the 95% CI equal to 0.985. The ratio of the specificities of cobas® HPV on the cobas® 5800 System and cobas® 6800/8800 Systems for the detection of ≥CIN2 was 0.999 with the lower limit of the 95% CI equal to 0.98. For reproducibility, percent coefficient of variation (%CV) across all the parameters examined were all under 2%. cobas® 5800 detected 100% of the panel members correctly.

Conclusions: The results demonstrate that cobas HPV on the cobas® 5800 is equivalent to the clinically validated cobas® HPV on the cobas® 6800/8800.

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#4823

Increase of cervical cancer prevention in the Czech Republic using self-sampling

10 - HPV screening

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Background/Objectives: The cervical cancer screening program is based on annual cytology with HPV triage in the Czech Republic. Screening HPV testing is covered by health insurance for all women aged 35 and 45 from 2021. The major challenge is the involvement of the women from a refractory population who do not attend the cervical cancer screening program for a long time. The objective of the study was to compare the different approaches to inviting women to the cervical cancer screening program.

Methods: The study was conducted in three arms. 6388 women from the database of dietary supplements company were included in the Arm A regardless of whether they participated in the cervical cancer screening program.Women who do not participate in the cervical cancer screening program for at least three years, and mostly had not previously reacted to several rounds of invitation, were selected from a database of a health insurance company (Arm B, 4813 women) and gynecologist database (Arm C, 653 women).EvalynBrush self-sampling devices (Rovers Medical Devices) were sent by Czech post to the women home address.All returned samples were analyzed using the Anyplex II HPV HR Detection kit (Seegene)/QIAscreen HPV PCR (Qiagen).

Results: The return rate was 7.6% (486/6388) in Arm A, 7.6 % (367/4813) in Arm B and 9.0% (59/653) in Arm C. HPV positivity was detected in 7.4% (36/486) of Arm A samples, 17.7% (59/334) of Arm B samples and 10.2% (6/59) of Arm C samples.

Conclusions: The return rate was highest in Arm C where the women were invited through their gynecologists. Based on these results, we are currently expanding Arm C to include additional 4000 invited women. The offering of self-sampling could significantly increase the attendance of Czech women in the cervical screening program. This work was supported by grants: IGA_LF_2022_012, Programme EXCELES (LX22NPO5103), LM2018133,CZ.02.1.01/0.0/0.0/16_019/0000868 and charity Cancer Research Czech Republic.

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#4765

Distribution of self-sampling device among Czech women targeted by the cervical cancer screening program

10 - HPV screening

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Background/Objectives: The implementation of primary HPV screening and increasing cervical screening participation are major challenges to cervical cancer screening in the Czech Republic. The offering of self-sampling to cervical screening non-attenders could significantly increase participation as was shown in several European countries. The objective of this study was to bring the pilot data about the acceptance of self-sampling by Czech women and to find out the high-risk HPV (hrHPV) prevalence in the screening population.

Methods: Evalyn® Brush self-sampling kits (Rovers Medical Devices) were distributed by mail between October 2019 and March 2020 to 6,388 women aged 30-65. Women were chosen regardless of their cervical cancer attendance. After the self-sampling, samples were returned free of charge by regular mail. All samples were tested for hrHPV DNA using the Qiascreen HPV PCR Test (Qiagen). Results were delivered to women by mail or e-mail with the recommendation to schedule the check-up regardless of their HPV status.

Results: The response rate in this study was 7.61% (486/6388). All samples were suitable for analysis using Qiascreen by which hrHPVs were detected in 7.47% (36/486) self-samples. Seven HPV16 (19.4%), one HPV18 (19.4%), and 28 other (77.7%) high-risk HPV-positive cervicovaginal samples were identified.

Conclusions: HrHPV was detected in 7.61% of women chosen from the cervical cancer screening population. The offering of self-sampling could significantly increase the attendance of Czech women in the cervical screening program. This work was supported by grants: IGA_LF_2022_012, CZ.02.1.01/0.0/0.0/16_019/0000868, Programme EXCELES, ID Project No. LX22NPO5103, LM2018133, and charity Cancer Research Czech Republic.

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#5575

Cervical human papillomavirus infection among vulnerable women in Rome, Italy: THE Dorothy project

11 - Screening for women difficult to reach

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Background/Objectives: Data on cervical HPV infection in vulnerable populations, such as migrant and homeless women, are scant. Indeed, these women suffer from reduced access to health services, as those aimed to secondary prevention of cervical carcinoma, which is the HPV-associated neoplasm with the highest incidence worldwide. The study aimed to acquire information about the epidemiology of HPV infection in fragile women, investigating prevalence and predictors of cervical HPV infection. Additionally, the level of knowledge about HPV and HPV vaccination was investigated.

Methods: Women were enrolled at the center for homeless people located at the main train station in Rome, Italy (Binario95) and in the Polyambulatory located under the colonnade of San Peter's square. They underwent to: i) an interview aimed to collect socio-demographic, behavioural and anamnestic data, and ii) a gynaecological examination during which a cervico-vaginal sample was collected in PreservCyt (Hologic). High-risk HPV test was performed by the Xpert-HPV (Cepheid).

Results: Between April and November 2022, 66 women were enrolled (median age: 47 years, range 21-68). Three women were Italian (4.5%), with the others coming from other European (19, 28.8%) or non-European countries (44, 66.7%). They reported a median of three and one lifetime and recent sexual partners, respectively. Three women (4.5%) had had ano-genital warts in the past. Of the 60 women who consented to the cervico-vaginal sampling, eight (13.3%) tested positive for high-risk HPVs, fifty had a negative cervical cytology (83.3%), six had an abnormal cytology (10.0%) and four had a not assessable cytology (6.7%). Around half of the women (36, 54.5%) had heard of HPV, and 24 of them (66.7%) knew that HPV infection is sexually transmitted. Overall, only 8 women (12.1%) had heard of the HPV vaccine. Once informed about HPV vaccination, 24 women (36.4%) declared to be willing to be vaccinated.

Conclusions: Among women, high-risk HPV prevalence seems to be higher than among Italian women, although a larger sample size is required to obtain robust estimates.

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#4785

Full genotyping and FAM19A4/miR124-2 methylation analysis in high-risk human papillomavirus-positive samples from women over 30 years participating in cervical cancer screening in Örebro, Sweden

12 - Triage of HPV positive women

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Background/Objectives: Currently, cervical cancer prevention is undergoing comprehensive development regarding human papillomavirus (HPV) vaccination and cervical cancer screening. In Sweden and many other countries, high coverage vaccinated cohorts are entering screening within the next few years. This entails demands for baseline HPV genotype data across the screening age range for surveillance and a basis for screening program adjustment. In 2016, Örebro County, Sweden, changed to primary HPV screening using HPV mRNA testing followed by cytology triage. An alternative triage method to cytology could allow for a fully molecular screening algorithm and be implemented in a screening program where self-sampling is included. Hypermethylation analysis of the human genes FAM19A4/miR124-2 has been suggested as a promising triage method.

Methods: HPV mRNA-positive screening samples (n = 529) were included and subjected to genotyping targeting a broad range of both low-risk and high-risk genotypes in addition to hypermethylation analysis of the two human genes FAM19A4/miR124-2. Data were connected to cytological and histological status and age.

Results: The most commonly detected genotypes were HPV31, 16, and 52 both in total and in only single infected samples, and in ≥HSIL samples, HPV 16 was the most common. In addition, HPV18 was one of the most common genotypes in high-grade squamous intraepithelial lesions (HSILs) samples. In relation to available vaccines, 26% of the women with histological HSIL or cancer (HSILs) tested positive for only hrHPV included in the quadrivalent vaccine and 77% of the genotypes in the nonavalent vaccine. The methylation rate was 28% in samples from women with no evidence of disease, with a considerably higher methylation proportion of 67% in ≥HSIL samples. Furthermore, hypermethylation of the targeted genes was associated with age, where older women were more likely to present with a positive test result independent of screening outcome. Furthermore, no HPV-related independently predictive factor for hypermethylation was found.

Conclusions: HPV genotyping in this study shows evidence that a relatively large proportion of histological HSILs will remain, even after age cohorts vaccinated with the quadrivalent, as well as the nonavalent, vaccine enter screening. Except for age, no HPV-related independently predictive factors for hypermethylation were found. Accordingly, age needs to be considered in development of future screening algorithms, if including triage with hypermethylation and HPV genotyping.

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#5649

HPV testing on self-collected vaginal and urine samples using Papilloplex® HR-HPV DNA assay

13 - Self-sampling

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Background/Objectives: For self-sampling to confer maximum value, validation of the device and assay combination is required. We evaluated the performance of the Papilloplex® HR-HPV DNA assay on self-taken vaginal samples collected using FLOQSwab (Copan) and urine samples using Colli-Pee (Novosanis) and compared performance to clinician-collected cervical samples for the detection of significant cervical disease.

Methods: A total of 600 women consented to the study which was conducted in 4 colposcopy centres in Europe according to the European VALHUDES protocol (clinicaltrials.gov-NCT04312737). After consenting, women provided a first-void urine sample (Colli-Pee, Novosanis) and a vaginal self-sample (FLOQSwab®, Copan) at the clinic. Subsequently a clinician taken cervical liquid based cytology (LBC) sample was obtained (Cervex-Brush, Rovers). Participants were aged 25-64 and all received colposcopy with biopsies taken if routinely indicated. Vaginal samples were transported dry to the laboratory and resuspended in 5 ml of ThinPrep® (~15% of participants) or eNat® (85% of participants). Nucleic acid extraction was performed using Quick DNA/RNA viral MagBead (Zymo Research). The Papilloplex® HR-HPV DNA which detects 14 hrHPV genotypes was performed according to the manufacturer instructions. HPV positivity was defined at ≤ 39 cycle threshold (Ct) values as defined by manufacturer. A posterior cut-offs were applied for vaginal (FAM≤36, HEX≤35, ROX≤32) and urine samples (FAM≤41, HEX≤37, ROX≤36). Absolute sensitivity and specificity of the assay was assessed for the detection of CIN2+, stratified by biospecimen type in addition to relative clinical sensitivity/specificity of the self-taken samples vs the LBC sample. Results associated with the vaginal sample resuspended in eNAT are presented in this abstract.

Results: Absolute sensitivity and specificity of the Papilloplex on vaginal samples was 0.95 (95%CI: 0.89-0.98) and 0.39 (95% CI: 0.34-0.45) for the detection of CIN2+. Respective sensitivity and specificity values for the urine samples were 0.84 (95%CI: 0.77-0.90) and 0.47 (95% CI: 0.42-0.52). Relative sensitivity and specificity of the vaginal sample vs the LBC sample was 1.05 (95%CI: 1.006-1.09) and 0.81 (95% CI: 0.74-0.89), whereas, for urine, these values were 0.93 (95 %CI: 0.86-1.00) and 0.93 (95%CI 0.87-1.004) respectively. Through performing a post-hoc optimisation of cut-offs relative sensitivity and specificity values of the vaginal sample were 1.00 (95%CI:0.95-1.05) and 0.93 (95% CI: 0.86-1.01). Comparatively, sensitivity and specificity values for urine sample at the adjusted cut offs were 0.95 (95%CI:0.88-1.01) and 0.95 (0.88-1.02)

Conclusions: We present data on the performance of an extended genotyping test on self-taken vaginal and urine samples taken within a colposcopy setting. While performance of the assay on the clinician and self-samples was similar, the data indicate that optimisation of cut-offs tailored to self-taken samples can enhance performance, particularly in terms of sensitivity.

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#5057

Copan universe permits automated preparation of vaginal self-collected swabs for HPV molecular testing

13 - Self-sampling

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Background/Objectives: UniVerseTM (Copan) is a fully automated pre-analytical system dedicated to preparation of specimens for molecular testing: tube vortexing, uncapping, recapping, managing of sample traceability and liquid transfer to secondary containers are the instrument's core activities. Recently UniVerseTM has been equipped with a liquid dispenser to automatically rehydrate vaginal self-collected swabs to permit downstream Human Papilloma Virus (HPV) molecular testing. The objective of this study is to demonstrate the equivalence of UniVerseTM with manual elution of HPV from dry swabs and to highlight the utility of UniVerseTM for automated pre-analytical process to support high volume population-level HPV screening programs.

Methods: PROCEEDxTM FLOQ® swabs (Microbix Biosystem) containing HPV 16 were used to simulate self-collected vaginal swab specimens for this experimental challenge. 20 PROCEEDxTM FLOQ® swabs were hydrated by UniVerse in 5ml of MSwab medium (Copan) and in parallel, 20 swabs were manually eluted and vortexed for 30 seconds in equivalent volume. Aliquots of specimen eluted in MSwab medium were analyzed using a molecular assay for the qualitative detection of HPV 16. Results were compared using the two one-sided test (TOST) to verify their equivalence (±2 Ct). Both methods allowed detection of HPV 16 with no significant difference in Ct values.

Results: UniVerse worflow provided a mean HPV 16 PCR Ct of 34.73 (Standard deviation 1.27; Coefficient of Variation: 3.67%; number of samples tested:20). Manual worflow provided a mean HPV 16 PCR Ct of 34.56 (Standard deviation 0.95; Coefficient of Variation: 2.75%; number of samples tested:20). The delta Ct between the two methods is 0.17 (95% C.I. -0.54÷0.89).

Conclusions: This study provides the proof of concept data for accurate detection of HPV with self-sampled vaginal swabs collected dry and subsequently eluted on the UniVerse and, demonstrates the equivalence between UniVerse and manual workflow. This ongoing study will integrate findings from a broader panel of contrived specimens representing self-collected swabs with vaginal matrix and HPV to investigate the potential use of dry transported swabs for HPV screening programs.

Bouska Ondrej
Czech Republic

#4813

Pilot study: involvement of long-term non-attending population of Czech women in cervical screening program

13 - Self-sampling

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Background/Objectives: Long-term non-attendance in cervical cancer screening is a common obstacle in decreasing cervical cancer morbidity and mortality. Addressed invitations for pre-scheduled check-ups or reminders of long-term non-attending cervical screening represent a possible way of increasing coverage of the unscreened population. Still, the direct distribution of self-sampling kits for human papillomavirus (HPV) testing is suggested to possess a better response for the involvement of non-attenders in cervical screening. This study aimed to bring the pilot data on the response rate for the addressed distribution of self-sampling kits for collecting vaginal/cervical samples from non-attenders in the Czech Republic.

Methods: In July 2021, Evalyn® Brush (Rovers Medical Devices) self-sampling devices were distributed to patients of one gynecological center in Olomouc. Only patients aged 30-65 who hadn´t attended a regular screening check-up for more than three consecutive years were enrolled. They were asked to collect vaginal/cervical self-samples in the comfort of their homes and send them back to the laboratory free of charge by regular mail or bring them personally. AnyplexTM II HPV HR Detection assay (Seegene Inc.) was used for high-risk HPV detection. Results of HPV testing were delivered directly to study participants with the referral to schedule the check-up regardless of their current HPV status.

Results: In total, 653 self-sampling devices were distributed. The response rate among non-attenders was 9,04 % (59/653), with 98 % of samples (58/59) returned within two months since the distribution of sampling devices. High-risk HPVs were detected in 10,2 % (6/59) self-samples. Two HPV16 (33,3 %), one HPV18 (16,6 %), and three other (50 %) high-risk HPV-positive cervical/vaginal samples were identified.

Conclusions: Direct distribution of self-sampling kits increased the participation of non-attenders in cervical screening in the pilot study cohort. However, the response rate remained lower than expected. Based on these findings, the pilot study was extended, and additional distribution of 5,000 self-sampling kits is ongoing to reinforce the importance of cervical screening in the Czech Republic.
This study was supported by the project ENOCH (CZ.02.1.01/0.0/0.0/16_019/0000868), the internal grant of Palacký University (IGA_LF_UP_2022_012), and the Cancer Research foundation Czech Republic.

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Central African Republic

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#4773

High acceptability and accuracy of self-collection by veil collector device for high risk-HPV screening by multiplex real-time PCR among adult women and men who have sex with men (MSM) living in Central Africa

13 - Self-sampling

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Background/Objectives: Cervical and anal cancers are caused by high risk-human papillomavirus (HR-HPV) infection. Self-collection of genital and anal specimens and HPV DNA molecular testing are methods increasing screening rates.

Methods: The practicability and acceptability of genital and self-collection method with veil (Veil Collector V-Veil Up UP2TM, V-Veil-Up Production SRL, Romania; https://hpv-veil.com) were assessed in female sex workers (FSWs) in Kisangani, Republic Democratic of Congo (DRC), adult women in N'Djamena, Chad, and men who have sex with men (MSM) in Yaounde, Cameroon. The accuracy of Veil Collector V-Veil Up UP2TM for HPV DNA detection was compared in subgroup of unselected women to clinician-collected endocervical swabs (as reference collection). Samples were conserved in medium Cyt-All (Alphapath, Mudaison, France). HPV DNA detection used AnyplexTM II HPV28 test (Seegene, Seoul, South Korea) or Papilloplex High Risk HPV (GeneFirst, Abingdon, United Kingdom).

Results: 415 FSWs (mean age, 28.1 years) in DRC, 253 women (mean age, 35.0 years) in Chad and 57 MSM in Cameroon were enrolled. In DRC, the prevalences of HPV and HR-HPV infections were 54.2% and 29.0%; two-third of HR-HPV would be covered by Gardasil-9® vaccine. In Chad, HPV and HR-HPV prevalences were 22.9% and 15.8%, respectively; 70% of HR-HPV were targeted by Gardasil-9®. In Cameroon, HPV and HR-HPV prevalences were 74.1% and 59.6%; 65% of HR-HPV would be covered by Gardasil-9® vaccine. Veil-based genital self-collection showed high acceptability (96%), feasibility and satisfaction, in DRC, Chad and Cameroon. In Chad, self-collection by veil was non-inferior to clinician-based collection for HR-HPV DNA testing, with "good" agreement, high sensitivity (95.0%; 95%CI: 88.3-100.0%) and specificity (88.2%; 95%CI: 83.9-92.6%). Remarkably, HPV DNA and HR-HPV DNA positivity rates were significantly higher (1.67- and 1.57- fold, respectively) when using veil-based collection method than clinician-collected endocervical swabs.

Conclusions: These observations highlight the high burden of cervical and anal HR-HPV infection in various high-risk populations living in Central Africa. The Veil Collector V-Veil Up UP2TM collection device would constitute a simple, highly acceptable and powerful tool for self-collection of genital and anal secretions for further molecular testing and screening of HR-HPV that could be easily implemented in national cervical and anal cancer prevention programs in Africa.

Meers Nette
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#4589

Validation of Colli-pee UCM FV-5004: a user-friendly device for volumetric first-void urine collection and HPV DNA preservation compatible with high-throughput instruments

13 - Self-sampling

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Background/Objectives: Colli-Pee® UCM® FV-5004 is a newly developed variant of the Colli-Pee® device. The tube has been designed for compatibility with high-throughput instruments (e.g. Roche Cobas, Hologic Panther, etc) facilitating in streamlining the pre-analytical process, shortening turnaround time, minimizing errors as well as reducing costs. The tube is pre-filled with UCM® preservative (1.4 mL), improving transport and storage of urine at room temperature, thereby enabling home-based sample collections. The aim of the study was to evaluate volumetric collection as well as urine preservation capabilities of Colli-Pee® UCM® FV-5004.

Methods: The unique device characteristic facilitating direct mixing of preservative and urine was evaluated by a mixing study. Furthermore, as part of performance validation of Colli-Pee® UCM® FV-5004, two studies were conducted. First, 22 healthy donors collected a first-void urine sample with the device, whereby the total collected sample volume was evaluated by pipetting. In the second study, urine preservation was evaluated. Colli-Pee® UCM® FV-5004 devices underwent three freeze-thaw cycles (-20°C to 50°C) to simulate transport conditions prior to collection. First-void urine samples were then collected from 10 female and 10 male participants. Each sample was spiked with HPV-16 plasmid DNA (~500,000 cps/mL), and stored at room temperature (RT; 20°C-26°C) until processing. At baseline (T0) and 8 days (T8) DNA was extracted (Qiagen QIAamp DNA Mini kit) from a whole urine aliquot of each sample, followed by HPV-specific qPCR (internal developed assay) to evaluate HPV DNA detectability and preservation in the samples.

Results: The mixing evaluation study demonstrated clear and visual direct mixing of the preservative and urine which ensures a homogenous first-void urine sample optimized for downstream molecular analysis. In the first performance study, all 22 samples were confirmed to be within specified volume collection range (between 3.0 to 5.0 mL), with an average of 3.81 mL (SD = 0.19 mL). All 20 plasmid-spiked samples from the second study had detectable HPV DNA at T8 (T8 qPCR Ct < No Template Control). Additionally, all samples had a ΔCt (T8 - T0) of ≤ 3.0. The average ΔCt value was -0.71 ± 0.86 SD, with a minimum value of -2.41, and a maximum value of 1.90.

Conclusions: Colli-Pee® UCM® FV-5004 is a user-friendly device that provides volumetric collection of first-void urine, and effectively preserves HPV DNA in spiked samples for up to seven days at room temperature. These features, combined with collection tube compatibility with high-throughput instruments, make the device a promising solution for large-scale HPV DNA testing applications.

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#5058

Performance of High Risk HPV Single Analyte and Multiplex Panel External Quality Controls for Verification of Extended Genotyping on the BD OnclarityTM HPV Assay

14 - Genotyping

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Background/Objectives: The development of extended (beyond HPV 16/18) and full genotyping Human Papillomavirus (HPV) assays has resulted in a demand for external control panels that can confirm assay performance across multiple high-risk genotypes. To address this need, Microbix Biosystems Inc. designed and developed high-risk HPV (HR HPV) whole-genome raw materials as liquid single analytes and multiplex panels in PreservCyt®. Single analytes: 16, 18, 31, 33, 39, 45, 51, 52, 66. Multiplex Panels: Panel 1 with HPV 16/18/45; Panel 2 with HPV 39/51/52; Panel 3 with HPV 31/33/66. The HPV multiplex samples were developed by using full length viral genomes and human cells, thereby including all possible diagnostic targets. Samples demonstrate 100% clinical sample equivalence and include human housekeeping genes. The objectives of this study were to confirm targeted performance of the three multiplex HPV panels with the BD OnclarityTM HPV Assay.

Methods: A working suspension was prepared for each multiplex panel in both PreservCyt® and BD SurePathTM by combining 1 ml of the panel with 1ml of the respective cytology medium. Each suspension was vortexed to ensure homogeneity prior to removal of aliquots for testing. Contrived specimens were prepared by adding different amounts of each suspension to the BD OnclarityTM HPV Liquid Based Cytology Diluent tube and tested on the BD ViperTM LT system. Each multiplex panel was assayed separately and in combination with individual HR HPV types to simulate different co-infection scenarios and examine the features of the BD Onclarity TM HPV Assay to report discrete individual HPV types (HPV 16, 18, 45) or genotype groups (group1: 33/58; group 2: 56/59/66; group3: 35/39/68).

Results: Both the qualitative detection and assay cycle threshold (Ct) values were examined for all contrived specimens. The results demonstrate equivalent performance of samples prepared in PreservCyt® and BD SurePathTM. The BD Onclarity TM HPV Assay correctly reported discrete HPV types (16, 18 or 45) when assayed separately or as part of Microbix Panel 1. The HPV types in Microbix Panel 2 (39/51/52) were reported as an aggregate under group 3 of the BD Onclarity TM HPV Assay. The HPV types in Microbix Panel 3 (31/33/66) were reported as an aggregate under group 1 (HPV 33) and group 2 (HPV66) of the BD Onclarity TM HPV Assay.

Conclusions: The results confirmed the performance of Microbix HR HPV multiplex panels on the BD Onclarity TM HPV Assay. Furthermore, the results demonstrated the broader utility of Microbix HR HPV single and multiplex panels for assay verification/validation, serve as known positive material for operator training/competency assessment and permit routine External Quality Control (EQC) of the entire analytical process (lysis, extraction, amplification and detection).

Benevolo Maria
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#4825

Assessment of transversal accuracy FOR CIN3+ lesions OF HPV genotyping using the BD onclarity HPV assay in cervico-vaginal samples from the NTCC2 study

14 - Genotyping

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

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

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

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

Dorofte Luiza
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#4593

HPV genotype in metastatic HPV induced penile squamous cell carcinoma

14 - Genotyping

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Background/Objectives: Penile cancer is a rare cancer with a prevalence of 0.1-1 per 100 000 men in developing countries. This type of tumor can be highly mutilating and has a high metastatic potential. Penile carcinogenesis involves two independent pathways, one related to HPV infection and another associated with inflammatory conditions. The objective of this study was to investigate HPV status in primary tumor and lymph node metastasis. We also assessed the prognostic value of HPV genotyping in penile cancer.

Methods: We investigated the presence of HPV DNA and genotype distribution in both primary tumor and inguinal lymph node metastasis in a cohort of 345 men treated for penile cancer at Örebro University Hospital, Sweden between 2009 and 2018. A total of 98 patients had lymph node metastasis at the time of diagnosis. HPV DNA detection and genotyping were performed by using the PCR method Anyplex II HPV28. To evaluate the association between HPV-status in primary tumor and metastasis with clinical variables Chi-Square test was used.

Results: The overall HPV prevalence was 42.6% (147/345). 140 tumors showed a high-risk HPV genotype: HPV16 (110), HPV18 (8), HPV31 (3), HPV33 (6), HPV35 (1), HPV39 (1), HPV45 (7), HPV51 (2), HPV52 (4), HPV56 (2), HPV58 (2) and HPV59 (1). In 9 out of the 140 tumors both low-risk and high-risk HPV genotypes were detected. Additional 7 tumors were positive for low-risk HPV genotype: HPV42 (3), HPV42 + HPV6 (1), HPV82 (1), HPV82 + HPV44 (1) and HPV53 (1). From the 98 patients with metastatic disease, 45 had an HPV related primary tumor while the remaining 53 were HPV negative. HPV 16 was the most frequently detected genotype in HPV positive cases that presented with metastasis (n=40) but even patients with HPV 18 (1), HPV 35 (1), HPV45 (1), HPV 52 (1) and HPV82 (1) had metastatic disease. In patients with metastatic HPV related tumors the same HPV genotype was found in metastasis in 36 cases. In 2 of the cases genotypes were different in metastasis. However, in the remaining 7 cases, the metastasis were HPV negative. No significant association was found between HPV-status in tumor or metastasis and pT stage, pN stage, or recurrence.

Conclusions: Approximately 43% of the penile cancers included in the present cohort were related to HPV infection. The same HPV genotype was found in both the primary penile tumor and the inguinal lymph node metastasis in 78% of cases with metastatic disease. No significant association was found between HPV-status in tumor or metastasis and tumor characteristics, indicating a limited value of HPV genotyping as a prognostic marker in penile cancer.

Sudenga Staci
United States

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#5580

CD39 and PD-1 expression on peripheral CD4+ lymphocytes is associated with anal pre-cancer among men with HIV

15 - Molecular markers

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Background/Objectives: Regulatory T cells (Treg) are responsible for the control of autoreactive lymphocytes and downregulate the immune response to tumor-associated antigen. The increased presence of Treg has been reported in the peripheral circulation for a variety of solid tumors, which presumably contributes to the suppression of an effective antitumor immune response. Among men that have sex with men (MSM) with HIV, we assessed differences in immune cells comparing those with and without anal pre-cancer.

Methods: MSM with HIV undergoing anal cancer screening using high resolution anoscopy and anal cytology were enrolled in the ALTO Study. Participants provided a peripheral blood mononuclear cells (PBMC) biospecimen. Phenotypic analyses of T lymphocytes were performed using flow cytometry. Specimens were thawed and stained for viability (live/dead Aqua), T cell subsets (CD3+, CD4+, CD8+), memory subsets (CD45RO, CCR7), and markers to identify Treg and T cell exhaustion. Treg were defined as CD4+CD25+FOXP3+, and "functional" Treg were identified by CD39 (an ecto-nucleoside triphosphate diphosphohydrolase) expression. CD39 (on non-Tregs) along with PD-1 were used to identify T cell exhaustion. Flow cytometry results were analyzed using the FlowJo program. We compared immune cell proportions (percent) between those with and without anal pre-cancer (HSIL vs normal and LSIL vs normal) using logistic regression.

Results: The study included six high grade squamous intraepithelial lesions (HSIL), 17 low grade squamous intraepithelial lesions (LSIL), and 16 with normal anal epithelium among men with PBMC. On non-Tregs, increasing proportions of CD4+CD39+ (OR=1.27, 95%CI= 1.03-1.57) and CD4+CD39+PD-1+ T cells (OR=1.40, 95%CI= 1.03-1.89) were associated with an increased odds of anal HSIL compared to those with normal anal epithelium (Figure). Increasing proportions of Tregs expressing PD-1 and CD39+ was also associated with an increased odds (OR=1.09, 95%CI= 1.01-1.18) of anal HSIL compared to those with normal anal epithelium. There were no statistically significant differences in immune cells proportions between LSIL and normal anal epithelium.

Conclusions: Among MSM with HIV, those with HSIL were more likely to have higher proportions of circulating exhausted T-cells and activated Tregs compared to men with normal anal epithelium, both of which could be contributing to low immune response to high-grade lesions. Measuring the frequencies of peripheral T cell phenotypes has the potential to help identify individuals at high risk for HSIL and identify individuals with more advanced lesions who could benefit from check-point inhibitor therapies.

Xinyue Li

Li Xinyue
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#5159

Comparison of various prognostic markers and HR-HPV expression in endocervical adenocarcinoma

15 - Molecular markers

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Background/Objectives: To study the expression of HR-HPV in different categories of endocervical adenocarcinoma (ECA) and assess the prognosis of various biomarkers.

Methods: We performed a retrospective analysis of 54 cases of ECA diagnosed pathologically in the Cancer Institute/Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College between 2005 and 2010. The pathomorphological categorization of ECA was performed according to the WHO classification of female genital tract cancers in 2020 and combination with p16 and PR staining. HR-HPV DNA and HR-HPV E6/E7 mRNA were detected using the SPF10-DEIA-LiPA25 system and RNAScope ISH techniques, respectively, in order to examine the distribution of HR-HPV DNA in ECA tissues. The distribution of HR-HPV DNA in adenocarcinoma lesion tissue was examined using Laser Capture Microdissection PCR (LCM-PCR), which was performed to fifteen randomly selected HR-HPV DNA-positive tissue sections.

Results: 30 of the 54 ECA cases were HPVA (HPV-associated adenocarcinoma) and 24 were HPV-I (HPV-independent adenocarcinoma), with HR-HPV DNA positive rates of 96.7 % and 33.3 %, respectively (c2=24.794, P<0.001). HR-HPV E6/E7 mRNA positivity was 63.3% in HPVA and all negative in HPV-I. The LCM-PCR results indicated that 5 of 15 ECA cases had HPV DNA positive and 10 were negative, which was consistent with the HR-HPV E6/E7 mRNA test results (Kappa=0.842, P=0.001). The sensitivity and specificity of HR-HPV E6/E7 mRNA were 64.8% and 55.6%, respectively, according to ROC analysis, with better diagnostic performance than WTS-PCR and p16 immunohistochemistry. The positivity of p16 in HPVA and HPV-I were 70.6% and 29.4% (c2=8.402, P=0.004). According to the Kaplan-Meier method analysis, there was no difference in the 3-year overall survival (OS) rate between patients with HR-HPV DNA positivity and those who were negative (Log Rank P=0.156), p16 positivity was associated with a higher 3-year OS rate than negativity (Log Rank P=0.038), and HR-HPV E6/E7 mRNA positivity was associated with a higher 3-year OS rate than negativity (Log Rank P =0.001).

Conclusions: The new WHO classification can better indicate the HPV infection status, when compared to WTS-PCR, p16 staining and HR-HPV E6/E7 mRNA can better express tumor with HPV and correlate with ECA prognosis.

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#4863

The immumohistochemical characteristics of cervical glandular intraepithelial neoplasias

15 - Molecular markers

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Background/Objectives: The aim of our study was to identify immunohistochemical diagnostic criteria for cervical glandular intraepithelial neoplasias (CGIN).

Methods: We examined 136 women with cytological diagnosis of atypical endocervical cells. These patients were divided into three groups based on a grade of the lesion: 35 patients with CGIN1 (group I), 72 patients with CGIN2 (group II), 28 patients with CGIN3 (group III). Endocervical curettages were examined by hematoxylin-eosin and immunohistochemistry using monoclonal antibodies against Ki-67, EpAg, MNF116, CEA, EMA. We used histological algorithm created by us.

Results: The comparative analysis of immunohistochemical results showed that expression of Ki-67 is seen in CGIN 2 and significantly increased in CGIN3 ($p<0,05$) which indicates increased proliferative activity of glandular cells in relation to increased grade of lesion. The differences in the expression of MNF116 and EMA are not statistically significant ($p>0,05$) which indicates that the expression of these epithelium specific markers does not change according to the grade of atypia and carcinogenesis (they can be used for determination of tumor phenotype). The expression of CEA and EpAg is strongly increased in CGIN2 and CGIN3 ($p<0,05$) indicating their potential role in carcinogenesis.

Conclusions: The results suggest that evaluation of a grade of cervical glandular intraepithelial neoplasia should be based on histological and immunohistochemical studies. The morphometric algorithm should include the following criteria: type of lining epithelium (cubical, columnar), nuclear cytoplasmic index (<1, >1, =1), stratification, hyper- and hypochromasia, size and amount of nucleoli, and stromal-parenchymal ratio. The immunohistochemical study should include the expression of proliferation marker (Ki-67), carcinoembryonc antigen (CEA)and Epithelial Antigen (EpAg). We recommend the classification of CGIN into two types: low grade cervical glandular intraepithelial neoplasia (CGIN 1) and high grade cervical glandular intraepithelial neoplasia including CGIN 2 and CGIN 3.

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#4819

Epistasis between GSTM1, NOS3 and MTHFR genes in cervical carcinoma or precursor lesions

15 - Molecular markers

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Background/Objectives: Cervical carcinoma is a malignant neoplasia in the uterus, originated from the high-risk Human Papillomavirus (HPV) infections. According to Global Cancer Observatory, this cancer represented about 3.1% of all malignant tumors in 2020, being the fourth most common cancer in women, and a great problem of global public health. NOS3 synthesizes nitric oxide (NO), a highly reactive molecule that can react in certain conditions with other ROS producing RNS (Reactive Nitrogen Species). The 27-bp VNTR 4a/b variant alters NOS3 expression and impairs NO synthesis. GSTM1 isoenzyme catalyses the conjugation of reduced glutathione (GSH) with any type of potentially toxic molecules, including products of oxidative stress. Its null variant causes lack of function and therefore impairs the ability to eliminate these products. Previously we have detected a protective effect of the 4a4a (NOS3) genotype and (+) GSTM1 in cervical cancer or precursor lesions (OR=0.089 and OR=0.594, respectively). Now we added the MTHFR gene to the study. MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine. Homocysteine is a precursor of glutathione. Its C677T polymorphism decreases its activity by 45% in 677CT genotype and up to 70% in 677TT genotype. Our purpose is to study the association of the C677T with the disease and the epistasis (interaction) between the three genes.

Methods: A total of 166 women were studied (94 healthy and 72 HPV infected).PCR-RFLP was used for MTHFR genotyping. Statistical analysis was made in SPSS with a level of significance of 0.05.

Results: No association with the disease was found with the MTHFR gene alone. However, we found a protective effect in the presence of both alleles: (+) GSTM1 and (C) MTHFR (p=0.028; OR = 0.500, CI (95%) = [0.268 - 0.932]). A protective effect was also found in the presence of both alleles: (+) GSTM1 and (4a) NOS3 (p=0.009) and a risk effect in the presence of both alleles: (-) GSTM1 and (4b) NOS3 (p=0.029; OR = 2.868, CI (95%) = [1.102 - 7.468]).

Conclusions: Our results show the importance of mechanisms related with ROS inactivation and oxidative stress in the predisposition for cervical cancer and its precursor lesions and reinforces the importance of the epistasis in genetic association studies.

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#4838

Evaluation of the clinical detection of the human papilloma virus using two validated platforms: second interlaboratory study in Argentina

16 - Screening methods

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Background/Objectives: The detection of high risk HPV (HR-HPV) DNA as a primary screening test is being gradually implemented in Argentina, as part of a comprehensive strategy for the prevention of cervical cancer. Like any other laboratory assay, the HR-HPV testing has to be monitored for continuous and rigorous quality assurance to avoid a sub-optimal, potentially harmful practice; it is essential to guarantee precise and accurate analyses to support optimal patient care. In this line, it is necessary to participate in external quality assessment programs to evaluate the performance of the laboratories and their competence; however, the participation in international programs is often expensive and panels are complex to import, so the local program is of great interest. A successful local interlaboratory study was launched in 2019 for the first time. Here, we report a second interlaboratory study conducted in July 2022 which included laboratories using two clinically validated platforms.

Methods: A panel consisting of 6 vials containing cervicovaginal cells in Preservcyt medium; each sample may contain either no HPV, a single HPV type or a mixture of HPV types at varying concentrations. The panel was tested 10 times to analyze its homogeneity; the acceptance criterion, considering 1 logs = 3.3 Cp (crossing point), was: trimmed mean of Cp±0.25 logs in 90% of the repetitions. Panels were sent to 30 laboratories that routinely use the HPV COBAS 4800 test (Roche) and RealTime High Risk HPV test (Abbott). The qualitative analysis was based on comparing the results (expressed as a dichotomous variable: detectable [D] or non-detectable [ND]), obtained by each participating laboratory, for each vial, using the EP12-A2 protocol of the Clinical and Laboratory Standards Institute (CLSI)

Results: The analysis of the results obtained by all participating laboratories showed a degree of agreement of 100% for positive and negative results.

Conclusions: The success of the call stands out; in this second opportunity, the number of participating laboratories grew from 12 (2019) to 30 (2022). All the invited laboratories agreed to participate and sent their results in a timely manner. An overall degree of agreement of 100% was obtained for positive and negative results. The study favors the establishment of a local external quality assurance program, allowing continuous monitoring of the performance of HPV tests in Argentina.

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#4714

Glandular and metaplastic transformation zone cells in cervical cytology decline with age

16 - Screening methods

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Background/Objectives: During the climacteric period, important changes occur in the morphology of the cervical epithelium and stroma due to hypoestrogenism, which can make the interpretation of cervical cytology difficult, as well as reduce its sensitivity. The presence of glandular and metaplastic cells in cytology has always been considered to be an important indicator of cervical smear quality. In the literature, higher detection rates of cervical intraepithelial lesions have been found in smears containing glandular and/or metaplastic cells. Thus, it is suggested that smears lacking these cells would be less sensitive to detection of dysplasias and cancer [1,2]. Due to these anatomical changes resulting from postmenopausal hypoestrogenism, the objective of the present study was to compare the presence of transformation zone cells (glandular cells and metaplastic cells) in the cervix of premenopausal and postmenopausal women.

Methods: A retrospective study assessing the results of cervical cytology smears collected at a private laboratory in São Paulo (Brazil) between January 2010 and December 2015 was performed. The study was approved by the local research ethics committee of the institution.

Results: A total of 1,030,482 cytology tests were performed between January 2010 and December 2015. Of these, 3,811 (0.36%) unsatisfactory samples were excluded, giving a total of 1,026.671 satisfactory cytology samples for assessment and inclusion in the statistical calculations. Of the satisfactory cytology samples, 60.6% had transformation zone cells (glandular and/or metaplastic) for interpretation (622,071), and 39.4% (404,600) did not have these cells. A marked decline in transformation zone cells with age was evident, with a greater decrease in the ≥ 50 years age groups ($p < 0.001$). Only 35% of women ≥ 50 years of age had transformation zone cells in cytology, while in those < 50 years, the figure was 67.5% ($p < 0.001$).

Conclusions: In the menopausal patient group, we suggest routine high-risk HPV DNA testing, given that this test is considered to be more sensitive for detecting cervical lesions in this group of patients.

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#5031

HPV genotyping and methylation test in the liquid-based cytology of rare genital and anal lesions

18 - Methylation

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Background/Objectives: Squamous cell carcinomas (SCC) of the cervix are almost 100% caused by long-term infection with high-risk human papillomavirus (HR-HPV) and the HPV test represents the most sensitive detection tool in cervical SCC screening. The methylation test detecting methylation silencing of certain cellular genes is then a highly specific marker of advanced dysplastic lesions. Both the above-mentioned genetic tests increase the diagnostic performance of cervicovaginal cytology and can be also used for selecting patients with high-grade squamous cell lesions for follow-up. The aim of our study was to evaluate the added value of the HPV test and the methylation analysis in the cytologically-based diagnosis of rare genital glandular and anal lesions.

Methods: A total of 50 liquid-based cervicovaginal cytology (LBC) samples with glandular-cell atypia in cytology and known histological diagnosis, and 74 anal LBC samples from HIV-positive men having sex with men (MSM) were retrieved from the archive of Biopticka laboratory. Classification of cytological findings was performed according to the third edition of the Bethesda classification, 2014. Molecular genetic analysis, which included three-target PCR genotyping of mucosal HPV types, and methylation analysis by QiaSure methylation test were performed on the residual LBC material.

Results: The most common findings of cervicovaginal cytology were atypical glandular cells, favor neoplastic (AGC-FN). The HR-HPV types were detected in 42/50 (84%) samples. The methylation test was positive in 45/50 (90%) samples. Both HR-HPV-associated and HR-HPV-independent glandular lesions were methylation-positive. 18 out of 20 women with methylation-positive AGC-FN had available follow-up histological examination, and in all of them, high-grade lesions were confirmed. The most common findings of anal cytology were low-grade squamous intra-epithelial lesions (LSIL). The HR-HPV types were detected in 42/74 (58%) samples. The methylation test was positive in 22/74 (30%) samples, however, 35/74 (47%) samples did not reach sufficient cellularity necessary for a valid result. Negative cytological findings were more prevalent among methylation-negative samples than methylation-positive samples (Fisher exact test, $p = 0.0367$).

Conclusions: A positive finding of HPV18, HPV16, and HPV45 in LBC was most commonly associated with an HPV-associated cervical glandular lesion. A positive methylation test with high sensitivity identified cervicovaginal smears that contained high-grade squamous cell and glandular cervical lesions and gynecologic malignancies of non-cervical origin such as endometrial carcinoma. In anal cancer screening, the HR-HPV positivity may help to select HIV-positive MSM for more intensive follow-up. The methylation test is still of limited use in anal cytology. The finding that methylation-positive patients were statistically more likely to have abnormal cytological findings suggests the promising potential of methylation markers for future research.

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#4945

Establishment of a high-throughput liquid handling platform for the detection of high-risk oropharyngeal cancer serum antibody profiles

20 - Serology

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Background/Objectives: HPV-driven oropharyngeal cancer (HPV-OPC) has replaced cervical cancer as most frequent HPV-associated malignancy in many countries. Especially in men in high Human Development Index (HDI) countries, the overall number of OPC cases has strongly increased in the last decades (~55,000 new cases in 2020), and will most likely continue to rise. In addition, these tumors display an increasing HPV attributable fraction (AF), with a predominance of HPV16. However, little is known about HPV-OPC in low-and middle-income countries (LMIC). Serum-based antibodies against the HPV16 early protein E6 are present up to several decades before cancer diagnosis, making them a strong prognostic biomarker with high sensitivity and specificity. Therefore, screening for E6 seropositivity may be beneficial for early detection and secondary prevention of HPV-OPC, and enables minimally invasive treatment options, maintaining the patient's quality of life.

Methods: To analyze large prospective cohort studies, or to perform screening studies for OPC, tens to hundreds of thousands of serum samples have to be analyzed due to the rarity of the disease. Multiplex serology is a suspension-array technology that enables the detection of serum-based antibodies using bead-coupled antigens of interest. However, the previously developed manual workflow has limitations in throughput and scale-up options. Our novel automated high-throughput sample processing workflow is realized by the liquid handling platform Biomek i7 (Beckman Coulter) which integrates additional devices (e.g. tube/plate scanners, an automated plate washer and plate shakers). External machines that are part of the automated Multiplex serology workflow include the magnetic bead platform KingFisherTM Flex (Thermo Fisher Scientific) for automated bead coupling, and the high-throughput flow cytometry-based reader FLEXMAP 3D® (Luminex) for signal detection. All of these are connected to a centralized server for data output and assay monitoring.

Results: -

Conclusions: The automated workflow enables not only a time and personnel saving performance of the Multiplex serology assay, it furthermore improves assay precision and data reproducibility. Moreover, the implemented devices create opportunities for workflow adaptability, while the automated data transfer enables data tracking, which is advantageous for screening studies and the analysis of large cohorts.

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#4425

Can AI-based colposcopy replace convetional screening tests for cervical intraepithelial neoplasia?

22 - Artificial Intelligence

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Background/Objectives: Recently, a lot of research on colposcopy image analysis based on deep learning is in progress. The classification accuracy of cervical intraepithelial neoplasia using deep learning is reported to be about 60-80%. The present study aimed to investigate whether deep learning-based colposcopy image reading could be a better predictor for HSIL compared to other screening tests such as cervical cytology or HPV test.

Methods: We retrospectively reviewed 987 patients who underwent colposcopy from 2017 to 2019 at Jeju national university hospital. The patients with missing cytology or HPV test were excluded. Adenocarcinoma in situ and invasive carcinoma were excluded due to their small numbers. The probability that colposcopy image is HSIL was calculated by the deep learning model trained on 20,000 photos which we had made in our previous study. To identify the predictors of pathologically confirmed HSIL, univariate analyses were performed using Fishers exact test for categorical variables and Students t test for continuous variables. To explore the relative contributions of the various factors, multivariate logistic regression analysis including cervical cytology, HPV test, and calculated HSIL probability by deep learning model was conduct.

Results: A total of 892 patients were analyzed. 89% of patients had cervical cytology results with ASCUS or worse. The patients with positive HPV test was 75%. The patients who underwent punch biopsy and Loop Electrosurgical Excision Procedure (LEEP) were 59% and 25%, respectively. For every 1% increase in the HSIL probability predicted by deep learning, the odds of HSIL increase by 2.4%. Independent predictors of HSIL on multivariate logistic regression were HSIL or ASC-H cytology (OR = 10.95), positive HPV (OR = 5.44), and HSIL on colposcopy image classification by deep learning (OR = 2.16): all $P < .05$.

Conclusions: Although HSIL prediction through deep learning of colposcopy images achieved statistical significance, it is not yet possible to replace the conventional tes such as cervical cytology or HPV test.

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#5451

A combination of Epigallocatechin gallate, Folic Acid, Hyaluronic Acid and Vitamin B12 reverses condyloma growth and improves cervical lesion in a young Caucasian woman

23 - Diagnostic procedures / management

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Background/Objectives: Human Papilloma Virus (HPV) represents a global threat to health, especially for women. HPV is a virus that infect mucosa, particularly the uterine cervix. In the case of cervical infections, HPV may establish a persistent infection, which exposes women to the risk of developing cervical cancer. Available treatments include surgery or topic solutions and creams, but a systemic approach is still unavailable. In the latest years, natural molecules such as Epigallocatechin gallate, folic acid, hyaluronic acid, and vitamin B12 are gaining importance as potential therapies for HPV infections and lesions.

Methods: A 22-year-old female patient attended our clinic in 2022 for the occurrence of vulvar condylomas near the vaginal opening and the urethral meatus, and with a PAP test revealing Low-grade Squamous Intraepithelial Lesion (LSIL). We performed a colposcopy, a Schiller test and HPV-DNA test for typing. Concomitantly, we prescribed a 3-month treatment with one tablet per day containing Epigallocatechin gallate (EGCG) 200mg, Folic Acid (FA) 400μg, Hyaluronic Acid (HA) 50mg, and Vitamin B12 1mg. After the treatment, we evaluated the patient again through objective exam, PAP test and colposcopy.

Results: The colposcopy revealed a full visible squamocolumnar junction, and two areas of white epithelium with regular mosaic pattern. The Schiller test highlighted two unstained quadrants in those areas, and a high-risk genotype emerged from the following HPV-DNA test. After three months of treatment with EGCG, FA, HA and Vitamin B12, the objective exam revealed that the condylomas had heavily improved, while the lesions were still classified as LSIL following PAP test. During the colposcopy, the Schiller test highlighted that one of the lesions was undetectable, while the other area exhibited a pale staining.

Conclusions: Oral treatment with a combination of EGCG, FA, HA and Vitamin B12 was efficient to reduce condylomas and LSIL lesions in 22-year-old women with a high-risk HPV genotype. Such combination of natural molecules may represent a new systemic approach to manage HPV infections, especially in young women.

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#4951

Effect of a coriolus versicolor-based vaginal gel for high-risk HPV clearance and cyto-normalization in a 44-year-old patient with HR-HPV persistence of more than 10 years

23 - Diagnostic procedures / management

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Background/Objectives: Human papillomavirus (HPV) infection is one of the most frequent sexually transmitted infections and high-risk (HR) oncogenic strains of HPV are behind virtually all cases of invasive cervical cancer. Although prophylactic vaccines are highly effective, they have no therapeutic effect. In this clinical case, a Coriolus versicolor-based vaginal gel treatment was assessed for HR-HPV clearance and cyto-normalization.

Methods: A clinical case of a 44-year-old woman, ex-smoker from 2018, who attended for a routine follow-up visit due to a history of persistent infection for 12 years with a HR-HPV strain and both low-grade and high-grade squamous intraepithelial lesions in the cervix and vagina. The patient was subjected to two excisional therapies (large loop excision of the transformation zone) in 2007 and 2009 and one cervical CO2 vaporization in 2013, plus another vaginal CO2 vaporization in 2014 which reduced the extension and grade of the lesions. The follow up of the case showed 4 years of viral persistence and intermittent appearance of HPV-linked cytological alterations. At the time of the visit, she presented low-grade cervical lesions and was positive for HR-HPV type 53. Therefore, a conservative treatment with the Coriolus versicolor-based vaginal gel was prescribed (1 cannula/day for 1 month + 1 cannula/alternate days for 5 months) in 2019.

Results: After several surgical procedures and a long history of HR-HPV persistency, the patient achieved complete cyto-normalization and HR-HPV clearance with a 6-month treatment period of the Coriolus versicolor based vaginal gel.

Conclusions: This clinical case shows that a conservative non-invasive treatment with a Coriolus versicolor-based vaginal gel can be a valuable therapeutic option to achieve the normalization of cytological alterations and HR-HPV clearance in a patient with a long history (12 years) of HR-HPV persistency after several excisional and destructive treatments.

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#4965

Correlation between colposcopic patterns and histological grade of VAGINAL intraepithelial neoplasia (VAIN): a retrospective cohort study

23 - Diagnostic procedures / management

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Background/Objectives: Vaginal intraepithelial neoplasia (VaIN) is a rare human papillomavirus (HPV)-related premalignant condition. VaIN lesions are diagnosed histologically through colposcopy-guided biopsies of suspicious areas, which often only expert colposcopists are able to identify. The present study aims to evaluate the accuracy of colposcopy in the diagnosis of VaIN of any grade.

Methods: We conducted a retrospective analysis on a cohort of 139 women diagnosed with LG-VaIN (VaIN1) and HG-VaIN (VaIN2-3) between 2010 and 2021 at the "Regional Referral Center for Prevention, Diagnosis and Treatment of HPV-related Genital Disorders", Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. All women had been referred to our center for an abnormal Pap smear, and had undergone a vaginal biopsy under colposcopic guidance.

Results: The distribution of the hystological grades of VaIN lesions was the following: 57 women were diagnosed with VaIN1 (41%), 47 (34%) with VaIN2 and 35 (25%) with VaIN3. Grade I abnormal colposcopic patterns were recorded in 72 (51.7 %) women, while grade II abnormal colposcopic patterns were found in the remaining 67 (48.3 %). Grade II abnormalities were more commonly observed in women with VaIN3 (OR 5.4 [95% CI 2.23-13.04]; P = 0.0002). However, we found a poor, non-statistically significant, association between colposcopic grade and histological findings of VaIN1 and VaIN 2 (OR = 1.16 [95% CI 0.526-2.571]; P = 0.70).

Conclusions: Colposcopy-directed biopsy plays an important role in detecting vaginal intraepithelial neoplasia. Our data show that major colposcopic abnormalities (grade II patterns) well correlate with the grade of vaginal lesions. However, a grade I colposcopic finding does not exclude HG-VaIN, especially VaIN2. An accurate colposcopic examination of all vaginal walls must be performed in all women with an abnormal Pap smear in order to recognize the correct site to biopsy.

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#4852

Clinical significance of cytological findings of atypical glandular cells: 10 years experience of a colposcopic referral centre

23 - Diagnostic procedures / management

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Background/Objectives: Atypical glandular cells (AGC) are found in less than 1% of cervical Pap smears, and are most common in women over 40 years of age (1,2). According to the 2014 Bethesda Nomenclature System for Cervical Cytology (3), glandular epithelial cell abnormalities include those not otherwise specified (AGC-NOS), those originating from endocervical cells (AGC-EC), those originating from endometrial cells (AGC-EM) and those favoring neoplasia (AGC-FN). The cytological diagnosis of AGC is burdened by a significant interobserver variability (4,5) and, as such, the clinical interpretation for the early detection of female genital tract glandular neoplasia remains a challenge (6,7). The purpose of this study was to report the experience of a colposcopy referral center in Northern Italy and specifically to identify clinical and histological features of patients with a cytological finding of AGC.

Methods: This is a retrospective observational study including a series of consecutive patients diagnosed with AGC on conventional Pap smears with or without coexisting squamous abnormalities, between 2012 and 2021 at the "Regional Referral Center for prevention, Diagnosis and Treatment of HPV-related Genital Disorders", Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano. All the patients underwent a colposcopy and endometrial assessment. Histologic samples were collected through endocervical curettage, cervical biopsy, cervical excision, and/or endometrial biopsy.

Results: A total of 239 patients with AGG were included. The mean age of the women included in the study was 47.9 years. Patients' characteristics are reported in Table 1. Among the 190 patients for whom both cervical and endometrial data was available, 160 (79.9%) had negative or benign histological results, including cervical and endometrial polyps. Only 30 (21.1%) patients received a diagnosis of neoplasia: 23 women were diagnosed with cervical squamous neoplasia (12%), 9 with cervical glandular neoplasia (4.7%), 10 with endometrial neoplasia (5.2%) and one patient presented with metastatic carcinoma (0.5%). Cervical histologic results, stratified for colposcopic appearance, are reported in Table 3. Colposcopic findings were negative in 72.7% cases of glandular neoplasia and only in 22.5% of cases of squamous neoplasia.

Conclusions: The clinical work-up of patients with AGC must include a cervical and endometrial assessment, given the heterogeneity of the possible underlying conditions, arising both from cervix and endometrium. In some cases cervical and endometrial conditions can coexist. Despite the lack of sensitivity in the detection of glandular lesions, colposcopy remains a cornerstone in the evaluation of these patients, especially in cases of squamous neoplasia. Further analysis may help identify the risk factors for the different conditions, such as age, HPV test, menopausal status, use of hormonal treatment or intrauterine device and abnormal uterine bleeding.

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#5116

Colposcopy in women aged 65 years and older with normal cytology and persisting HPV infection

25 - Colposcopy

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Background/Objectives: Background: In 2020, cervical cancer screening in Germany has changed from a solely cytology based to a combined HPV and cytology-based strategy for all women aged 35 and older. Within the screening algorithm all women with persisting high-risk HPV infection >12 months undergo a colposcopic evaluation of the cervix. However, in elderly women the transformation zone is often hidden, and colposcopy might not be the ideal diagnostic procedure for these women. Generally, information about the prevalence of HPV high-risk infection and associated pre-malignant lesions in women aged 65 and older is limited. Aims: Our study aims to evaluate the role of a persistent high-risk HPV infection without cytologic changes in women aged 65 and older. What are the colposcopic findings? How often are histologic changes detected? Does a high-risk HPV infection play a similar role as in younger women?

Methods: Patients and methods: In 2020 25131 women underwent their first co-testing in the cytology laboratory "Kühler-Obbarius". Out of these women, 4327 where aged 65 and older. 119/4327 (2.8 %) women were HPV positive. Out of those, 114 appeared for a repeat co-testing in 2021. 61/114 (53.5 %) were persistently HPV high-risk positive. 45 of those women had again a normal PAP smear (NILM). To increase the number of patients with persistent HPV infection but NILM cytology we looked at 211 patients aged 65 and older with persistent HPV infection and normal cytology who presented for colposcopy at four certified centers in Hamburg, Kiel and Munich Jan 2021 until April 2022. We assessed their colposcopic findings, HPV subtypes when available, histology and p16/Ki67 staining. We also assessed repeat cytology and histologic results of excisional procedures when performed.

Results: Results: 87.7 % of the women had a type III transformation zone. 88.2 % (186/211) of all women had a biopsy taken (thereof 163 ECCs). In 25 (11.8%) women no sample was taken due to an inaccessible cervix, pain during examination or obliteration of the cervical canal. When a biopsy was taken; CIN II+ was detected in 10.8% (20/186). Out of those with CIN II+, 50 % where HPV 16 positive. Taking only the women diagnosed with CIN III or AIS into account 75% were HPV 16 positive. 85% of the women with CIN II+ had an abnormal cytology when taken during colposcopy.

Conclusions: Conclusion: A persistent HPV Infection in women aged 65 and older is generally rare with less than 3 %. With > 85 % type III TZ colposcopic evaluation is difficult and might not be the right diagnostic tool in this age group.

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#4868

Overtreatment rate after immediate local excision of suspected cervical intraepithelial neoplasia: A prospective cohort study

25 - Colposcopy

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Background/Objectives: Background: The gold standard of cervical intraepithelial neoplasia (CIN) treatment is large loop excision of the transformation zone (LLETZ) after histopathological diagnosis from punch biopsies. In addition, treatment may be appropriate at initial colposcopy. Our objective was to study the applicability of immediate treatment strategy according to clinical parameters.

Methods: Methods: We conducted a prospective cohort study among patients referred to colposcopy at Helsinki University Hospital, Finland, between January 2014, and September 2018 (ISRCTN10933736). Patients treated with LLETZ, either after biopsies or immediately at initial colposcopy, were included. The main outcome measure was overtreatment (OT) rate defined as normal or low-grade histopathological findings in LLETZ specimen within both treatment groups.

Results: Results: A total of 572 patients treated with LLETZ were included: 360 treated after biopsies and 212 treated immediately at initial colposcopy. When LLETZ was performed immediately after high-grade referral cytology and with colposcopic impression of high-grade disease, the overtreatment (OT) rate was 10.0% (95% CI 9.10 to 17.2), whereas when LLETZ was done after biopsy-confirmed high-grade lesions, the OT rate was 18.9% (95% CI 14.7 to 23.7), resulting in risk difference (RD) -8.91% (95% CI -16.0 to -1.82). Among HPV16/18 positive patients the OT rate was 8.22% (95% CI 3.08 to 17.0) for immediate treatment, resulting in RD of -10.7% (95% CI -18.3 to -3.04) compared to LLETZ after biopsies.

Conclusions: Conclusion: Immediate LLETZ does not result in overtreatment when applied on selected cases, especially after high-grade referral cytology and when high-grade lesion is also colposcopically suspected.

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#4790

On-line certification platform for colposcopists engaged in cervical cancer screening programme in Poland

25 - Colposcopy

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Background/Objectives: Coverage and quality at each step of cervical cancer screening are the most important factors determining its effectiveness. In the last decade substantial progress has been made in quality assurance (QA) of colposcopy in many parts of the world. Certification may be a part of a comprehensive QA process in colposcopy. Here we present a description of an on-line certification platform for colposcopists working in CC screening in Poland and initial results from its roll-out phase.

Methods: Each year new set of single-choice questions based on cases including colpophotograms and clinical data, selected and agreed on by country-renowned experts in colposcopy are implemented into the platform. Colposcopists log into the platform and answer randomly presented questions within seven days without the possibility to reevaluate already answered questions. By now, two editions were performed, in 2020 and 2021. The platform also contains an educational part consisting of cases e.g. from previous editions. Participation is voluntary but will be obligatory from 2025 for all colposcopists working in the screening programme in Poland.

Results: 8 and 26 colposcopists undertook voluntary certification in 2020 and 2021 respectively. Min., max. and average scores were: 41,47%; 85,10% and 59,16% in 2020 and 44,03%; 81,27% and 70,73% in 2021 respectively.

Conclusions: The use of an on-line certification platform for colposcopists is feasible in Poland as a part of the QA process. Obligatory participation should result in a full up-take of the platform among colposcopists who wish to work in the screening program. Because certification results below 50% occur, continuous training of colposcopists is required. Comparing results from certification platform with real-life colposcopy performance indicators in the screening program will make it possible to find out whether certification scores correlate with clinical performance.

Colposcopy

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#4645

Different approach to colposcopic findings in pregnancy

25 - Colposcopy

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Background/Objectives: Background: Colposcopy during pregnancy is challenging due to pregnancy-induced modifications of cervical anatomy, such as endocervical glands hyperplasia, cervical hyperemia and contact bleeding, that can mimic the appearance of invasive cervical cancer, especially in the third trimester. (1,2,3)

Methods: Case report: An asymptomatic 33 year-old woman had the regular Pap test performed and it was read as IIIb-HSIL. She was reffered to colposcopy examination that revealed widespread mosaic and punctations. The colposcopy-guided biopsy detected cervical intraepithelial neoplasia grade III. Therefore, the patient underwent radio wave cone biopsy. Histopathological analysis revealed low-grade squamose intraepithelial lesions with negative resection margins. The first colopscopy check-up, 4 months after cone biopsy, showed no colposcopic finding and Pap test was read as II NILM. At that moment the patient was 6 weeks pregnant. During pregnancy there was no vaginal bleeding and cervical length measured by ultrasound was normal. However, during collecting cervical bacteriological swab in 34 week of pregnancy, a macroscopically visible abnormality was noticed on the anterior lip of cervix. It was described as ulceration covered with fibrin debris and resembled invasive cervical cancer. A colposcopy expert has undertaken the examination and the finding was described as leukoplakia bordered by aceto-white epithelium with irregular borders. The colposcopist`s conclusion was that the abnormality presented ectopic endocervical glands hyperplasia. Taken in mind that the patient was in the third trimester, the Pap test showed no cytologic abnormalities, HPV DNA-PCR testing was negative and the colposcopic finding did not suggest invasive disease, biopsy was not undertaken. The pregnancy ended with term vaginal delivery, without cervical lesions. Colposcopy check-up was performed 6 weeks after the delivery, cervix was covered with squamose epithelium and there were no abnormalities.

Results: There is no section "results" as this is a case report research paper

Conclusions: Conclusion: Assesment of abnormal colposcopic findings in pregnancy should be done by experienced colposcopist in order to avoid invasive procedures that could lead to pregnancy complications.

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#4774

Predictors of treatment failure for adenocarcinoma in situ of the uterine cervix: Up to 14 years of recorded follow-up

26 - Cervical neoplasia

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Background/Objectives: The incidence of adenocarcinoma-in-situ (AIS) of the uterine cervix is rising, with invasive adenocarcinoma becoming increasingly common relative to squamous cell carcinoma. The present study reviewed a cohort of 84 patients first-time treated by conization for histologically-confirmed AIS from January 2001 to January 2017, to identify risk factors associated with recurrent/persistent AIS as well as progression to invasive cervical cancer.

Methods: Nearly 80% of the patients were age 40 or younger at conization. Endocervical and ectocervical margins were deemed clear in 42 of the patients. All but two patients had ≥1 follow-up, with post-conization high-risk human papilloma virus (HPV) results documented in 52 patients. Altogether, 12 histopathologically-confirmed recurrences (14.3%) were detected; two of these patients had microinvasive or invasive carcinoma. In three other patients cytology showed AIS, but without recorded histopathology. Eight patients underwent hysterectomy for incomplete resection very soon after primary conization; they were not included in bivariate or multivariate analyses.

Results: Having ≥1 post-follow-up positive HPV finding yielded the highest sensitivity for histologically-confirmed recurrence: 87.5 [95% confidence interval (CI) 47.4-99.7]. Current or historical smoking status provided highest specificity: 94.4 (95% CI 72.7-99.9) and overall accuracy: 88.0 (95% CI 68.8-97.5) for histologically-confirmed recurrence. With multiple logistic regression (MLR), adjusting for age at conization and abnormal follow-up cytology, positive HPV18 was the strongest predictor of histologically-confirmed recurrence ($P<0.005$). Having ≥2 positive HPV results also predicted recurrence ($P<0.02$). Any unclear margin yielded an odds ratio 7.21 (95% CI 1.34-38.7) for histologically-confirmed recurrence adjusting for age, but became non-significant when including abnormal cytology in the MLR model.

Conclusions: The strong predictive value of HPV, particularly HPV18 and persistent HPV positivity vis-à-vis detected recurrence indicated that regular HPV testing for patients treated for AIS is imperative. In conclusion, furthering a participatory approach, including attention to smoking with encouragement to attend needed long-term follow-up, can better protect these patients at high risk for cervical cancer.

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#4760

Distribution of NK cells in microenvironment during the progression of cervical intraepithelial neoplasia

26 - Cervical neoplasia

Background/Objectives: NK cells, Toll like receptors (TLRs), Langerhans cells and T cells play an important role in the protection of host organism from human papilloma virus infection. The aim of our study was to analyze NK cells, Langerhans cell density and Toll like receptors (TLRs) and Lymphocytic infiltration in the progression of cervical intraepithelial neoplasia.

Methods: Archival formalin-fixed and paraffin-embedded tissue samples, diagnosed as CIN or in situ CA, between 2015-2018 years. Study cohort included 20 cases with normal cervical tissue, 31 cases of CIN1, 24 cases of CIN2, 26 cases of CIN3 and 42 cases of in situ carcinoma, and 35 cases of invasive cervical carcinoma, altogether 178 cases. The age of patients varied from 30 to 50 years. Immunohistochemistry: 4μ FFPE tissue sections were deparaffinized in xylene and rehydrated by using serial dilutions of ethanol (96%, 80%, 70%) and heat mediated antigen retrieval has been performed. Antibodies against the following antigens were used: Ki67, BCL2, TLR9, CD1a, CD56, CD3, CD4 and CD8. Lymphocyte counts were analyzed in 20 high power fields (HPF) per case. We have calculated the NK cell epithelial index meaning the ratio between 100 epithelial cells and5 CD56 positive NK cells and Langerhans cell epithelial index meaning the ratio between 100 epithelial cell and CD1a positive Langerhans cells. The ratio 0.1-0.2 was considered as low, the ratio 0.3-0.5 was considered as moderate and the ratio >0.5 was considered as high. In addition, immune cell proliferation apoptotic index was calculated as the proportion of Ki67 and BCL2 positive cells as following: the number of Ki67 positive immune cells were divided into the number of BCL2 positive cells and the index was recorded.

Results: The results of our study indicated that CIN1 which subsequently progressed into CIN2 was characterised with low NK cell infiltration, high proliferation index and low apoptotic index. Similar results were seen in cases of CIN2 which were later progressed into CIN3 or in carcinoma

Conclusions: NK epithelial and Langerhans epithelial index can be used as an additional marker for the progression of CIN, we think that the assessment of proliferation apoptotic index of lymphocytes more accurately reflects the functional state of the immune system during HPV infection and this characteristic might be also well used as an additional criterion for the assessment of CIN progression potential.

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#4924

Sequencing of HPV-positive and negative vulvar carcinomas using the Oncomine Comprehensive Assay

27 - Vulvar diseases and neoplasia

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Background/Objectives: Vulvar carcinoma is a rare gynecological disease caused either by HPV or by effects of chronic inflammation. The mutational frequencies and landscape for HPV-positive and HPV-negative tumor development are supposedly two distinctly different pathways and early studies have revealed p53 alterations as drivers for HPV-negative tumors. Recently, the methodological improvement of next generation sequencing (NGS) has provided tools for looking closely into mutated genes, gene fusions and copy number alterations (CNVs). Despite a technical development the mutational landscape of vulvar carcinomas is not fully understood. With more detailed knowledge on target biological mechanisms, this group of patients could potentially be given individual treatment and monitoring.

Methods: Thirty-two (32) vulvar squamous cell carcinomas (formalin fixed paraffin embedded, FFPE) from 1988 to 2008 were included in the study. Of included cases, 16 were HPV-positive and 16 were HPV-negative. HPV-positive tumors were positive for HPV16 (n=13), HPV33 (n=1), HPV56 (n=1) and HPV59 (n=1). Included cases had a tumor cell average of between 25-75%. All cases were sectioned in parallel, 1 x 10 µm each, for DNA and RNA extraction and nucleic extraction was performed on the MagLEAD 12gc. The OncomineTM Comprehensive Assay v3 (ThermoFisher Scientific) was used to detect variants across 161 different tumor relevant genes. Ion reporter was used for evaluating sample results for hotspots, single nucleotide variants (SNVs), indels (insertions or deletion of sequences), copy number variants (CNVs) and gene fusions. Derived sequences were aligned to DNA reference library hg19 (Human(hg19)).

Results: From the included samples (16 HPV-positive and 16 HPV-negative vulvar squamous carcinomas), complete DNA and fusion results were available from 8 HPV-negative cases and 15 HPV-positive cases. Totally 143 unique variants were detected in the vulvar squamous carcinoma cases. The median number of variants per sample detected in the HPV negative group is 2,5 variants compared to 1 variant in samples in the HPV positive group, three cases in the HPV negative group have ≥ 10 variants. More HPV-positive tumors (n=13/16, 81%) presented with CNVs compared to HPV-negative tumors (n=6/11, 55%). Thirty CNV were found in HPV-positive tumors and 14 CNVs were found in HPV-negative tumors. This difference was not significant (Student´s T-test p=0.404). The most frequent CNV overall was cMYC, that was detected in 13 tumors, followed by CDK2 (n=5) and CDK4 (n=4). Three samples were shown to be carrying fusion genes, the TBL1XR1(1) - PIK3CA(2) fusion was found in two cases (one HPV positive and one HPV negative case), and the NF1(5) - PSMD11(2) fusion was found in one HPV positive case.

Conclusions: More unique genomic variants were detected among HPV-negative samples while HPV positive cancers revealed to have more CNVs. This group of rare tumors need to be further explored in larger studies and data evaluated with clinical outcomes to better identify markers for cancer development and treatment.

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#4845

High-grade vaginal intraepithelial neoplasia and recurrence risk: analysis of an Italian regional referral center series

27 - Vulvar diseases and neoplasia

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Background/Objectives: Vaginal intraephitelial neoplasia (VaIN) is a rare HPV-related premalignant disease. There is no consensus regarding the best treatment modality for VaIN. At present, LG-VaIN is managed conservatively since the rate of spontaneous regression is high, whereas progression to malignancy is extremely infrequent. On the other hand, HG-Vain is generally treated, given its higher rate of progression to vaginal cancer. Treatment options include ablation, excision, vaginectomy or the use of topical agents. Current evidence supports personalized treatment based on individual factors such as patients' age, site and size of the lesions, involvement of the vaginal vault, previous treatments and physicians' experience. The main aim of this study was to investigate the long-term risk of disease recurrence in women treated for high-grade vaginal intraepithelial neoplasia (HG-VaIN).

Methods: We conducted a retrospective analysis on a cohort of 82 women diagnosed with HG-VaIN between 2010 and 2021 at the "Regional Referral Center for Prevention, Diagnosis and Treatment of HPV-related Genital Disorders", Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. All women underwent either ablative treatment (CO2 laser ablation or electrocoagulation) or cold-knife excision.

Results: In our series, the recurrence rate following treatment was 17%. The 5-year cumulative probability of recurrence was 30.4% and the median time to recurrence was 15.5 months. None of the patients progressed to invasive vaginal cancer during follow-up. A concomitant cervical or vulvar intraepithelial lesion was significatively associated with an increased risk of recurrence (p=0.006).

Conclusions: The results of our study suggest that women with HG-VaIN are at high risk of developing disease recurrence after treatment, especially patients with a concomitant cervical or vulvar intraepithelial lesion. In these women strict monitoring is mandatory to obtain an early identification of recurrence.

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#4963

Anal high-grade intraepithelial neoplasia in women with cervical high-grade intraepithelial neoplasia

28 - Anal neoplasia

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Background/Objectives: Anal high-grade intraepithelial neoplasia (AIN2-3) is the precursor of HPV-related anal cancer. Although anal cancer is rare, its incidence is rising, especially in women. Women with high-grade cervical neoplasia (CIN2-3) or HPV-related genital cancer are at increased risk of developing AIN. Other risk groups include people living with HIV, immunocompromised patients, and Men who have Sex with Men (MSM).

Methods: The objective of this monocentric prospective study was to analyze the prevalence of AIN2-3 among women treated for CIN2-3. Exclusion criteria were: age < 25 years, previous HPV vaccination, immunosuppression, HIV infection and a history of anorectal cancer. All patients enrolled in the study underwent anal cytology and anal high-risk HPV-DNA testing (aHPV-DNA). If one or both tests were positive, a high-resolution anoscopy with biopsy of suspicious lesions was performed. All women also completed a questionnaire on sexual habits.

Results: A total of 100 women were enrolled between 2019 and 2021. Among these, eight patients had a concomitant or past diagnosis of anogenital warts, while one patient had a previous diagnosis of VaIN-HSIL. Anal Pap smears were positive for low-grade lesions in three patients, while 73 women tested positive for aHPV-DNA. Histological examination revealed the presence of AIN2-3 lesions in four patients, who subsequently underwent excisional treatment. Although 50% of aHPV-DNA-positive women reported having anal intercourse, as many as 45% of these declared they used condoms.

Conclusions: Women with CIN2-3 are at high-risk of developing AIN2-3, although to date no recommendations regarding prevention and treatment of AIN in this group of patients are available. Barrier methods aren't always effective to prevent anal HPV infection, probably due to the fact that the cervix is a reservoir of the infection.

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#4972

Anal Precancer Detection by High-resolution Microendoscopy by Combined with HPV Testing

28 - Anal neoplasia

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Background/Objectives: In the United States, the effectiveness of anal cancer screening programs has been limited by a high patient lost-to-follow-up rate between diagnosis and treatment of high-grade squamous intraepithelial lesions (HSIL), the anal cancer precursor [1]. New methods to identify HSIL in real-time may reduce loss to follow-up by facilitating "see and treat" approaches and may be valuable in resource limited settings. The high-resolution microendoscope (HRME) is a portable, battery-powered, low-cost, fluorescence microscope coupled to a fiberoptic probe used to image squamous epithelial nuclei following topical application of a fluorescence contrast agent (proflavine). The HRME is deployed with a multi-task network (MTN) that analyzes image data and provides a likelihood of an HSIL diagnosis [2]. In this work, we extend the MTN to incorporate patient human papillomavirus (HPV) status as an input.

Methods: Uterine cervix HRME images from a high-risk population were used to develop the MTN+HPV model [2]. Patients were stratified into three categories based on their cobas 4800 HPV test results: 1) HPV 16/18+ / Other±, 2) HPV 16/18- / Other+, and 3) HPV 16/18- / Other- which was then incorporated as a feature vector in the updated model (Figure 1). The multimodal vector was processed by a new fully-connected and softmax layer that generated the final precancer probability. The model was then tested in anal HRME images of people living with human immunodeficiency virus (HIV) with known HPV status from a prospective screening study.

Results: The anal study enrolled 77 patients of which 62 had valid HPV and HRME imaging data (Benign 12; LSIL 20; HSIL 30). Although incorporating patient HPV test results in the MTN was not associated with a substantial difference in model AUC, there was increased specificity at higher sensitivity values (Figure 2). At a sensitivity of 0.90, the HPV+ model was associated with a specificity of 0.67 versus 0.47 for the non-HPV model.

Conclusions: Incorporating high-risk HPV test results into an HRME image interpretation algorithm for anal HSIL diagnosis increased specificity, a desirable test characteristic, as these results would be used to guide treatment decision-making. This computer-assisted diagnostic tool, coupled with its portability and low-cost, make this a potentially useful option for community-based anal neoplasia surveillance. Randomized evaluation of these algorithms is warranted.

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Figures

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#5112

Circulating tumour HPV16 DNA at the commencement and completion of the radiotherapy in patients with p16 positive oropharyngeal cancer included in the ARTSCAN III study.

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The aim was to determine levels of circulating tumour HPV16 DNA (ctHPV16 DNA) before and after treatment in patients with p16-positive oropharyngeal squamous cell carcinoma (OPC) included in the ARTSCAN III study (1) and to assess the correlation of ctHPV16 DNA levels with tumour volume and outcome.

Methods: During the trial, blood samples were collected at the beginning and end of radiotherapy. ctHPV16 DNA was analysed in all patients with p16-positive OPC. The viral load of ctHPV16 DNA was determined with real-time PCR. The median follow-up was three years.

Results: Of the 138 patients with p16-positive OPC, 105 had detectable ctHPV16 DNA at the beginning of the treatment. There was a significant correlation between ctHPV16 DNA and the gross tumour volume (GTV) assessed for the primary site and nodes, $p<0.001$, $\rho=0.39$. Patients with ctHPV16 DNA levels below the median value of 65 copies/mL at the beginning of the treatment had a significantly better progression-free, $p=0.014$, and overall survival, $p=0.015$, compared with patients with levels above the median value. Patients with no detectable ctHPV16 DNA at the end of treatment had a favourable progression-free survival (PFS) compared to patients with ctHPV16 DNA residues, and that gain was most pronounced in patients with initial ctHPV16 DNA levels below 65 copies/mL. ctHPV16 DNA levels and tumour volume were independent factors for PFS in a multivariate Cox regression model including age, smoking status, haemoglobin, and treatment arm.

Conclusions: In patients with detectable ctHPV16 DNA at the commencement of the treatment, the level of ctHPV16 DNA is correlated with GTV. High levels of ctHPV16 DNA at the beginning of treatment and any residues of ctHPV16 DNA at the completion of treatment seem to negatively affect the outcome. Moreover, ctHPV16 DNA levels may provide additional information to known prognostic factors.

References: 1. ARTSCAN III: A randomized phase III study comparing chemoradiotherapy with cisplatin versus cetuximab in patients with locoregionally advanced head and neck squamous cell carcinoma. Gebre-Medhin et al J Clin Oncol, 2021 Jan 1;39(1):38-47

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#5017

High Risk HPV in HIV-Infected Women - a case report

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: HIV-infected women are at increased risk for infection with human papillomavirus (HPV) and thus development of HPV-related cancers. It is therefore important for clinicians to screen patients who are HIV-positive women routinely and a closer follow up.

Methods: We report a case of HIV-positive women with laryngeal squamous cell carcinoma and premalignant cervical lesion.

Results: 53-year-old female patient infected with both HIV and HCV, on HAART with a good virological and immunological response, with history of druge abuse and smoking. This patient was diagnosed with laryngeal squamous cell carcinoma with extranodal extension, and underwent a total laryngectomy, lymph node dissection and tracheostomy (figure 1). She was sent to our deparment with cervical cancer screening reporting low-grade squamous intraepithelial lesion and high-risk HPV (others than 18 or 16). After 6 months a follow-up cytology test reveled high-grade squamous intraepithelial lesion and high-risk HPV and colposcopy revealed type 3 transformation zone and lesions grade 2 (figure 2 and 3). Large loop excision of the transformation zone was perfomed and the histopathological report show high-grade squamous intraepithelial lesion, without endocervical glandular involvement A post-treatment colposcopic and cytology assessment at 6 months was performed and the result was negative for intraepithelial lesion or malignancy and negative HPV.

Conclusions: Studys reported that the percentage of HPV infection in patients with laryngeal pathology is around 13.2-25%. It is possible that HPV plays a relevant role in the etiopathogenesis of laryngeal cancers, particularly in females. In this case, it cannot be excluded that the laryngeal tumor is a consequence of a possible infection with the same HPV. Primary prevention and literacy promotion, especially in at-risk individuals, may increase the early detection of cancer, with an impact on survival and quality of life.

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#4853

Initial findings: a comprehensive meta-analysis of the sociodemographic factors associated with head and neck cancer by HPV status

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The association between sociodemographic variables such as race, gender, smoking history, and human papillomavirus positive (HPV+) head and neck cancer (HNC) has been well documented. The association between other sociodemographic factors, including alcohol use, marriage status, history of oral-genital sex, among others, with the development of HPV+ head and neck cancer has not been assessed comprehensively. Attempting to analyze these factors on a large scale can identify positive associations that may not be significant in smaller studies.

Methods: A comprehensive search strategy was utilized in PubMed, Scopus, and CINAHL for articles published in English through October 2022. Included studies were written in English and assessed sociodemographic factors in HNC patients stratified by HPV status. A total of 2752 studies were identified, with 23 meeting initial inclusion criteria. A meta-analysis of proportions and odds ratios was performed using MedCalc Software to determine associations between various sociodemographic variables and HNC by HPV status.

Results: A total of 80,089 patients were included with 46,046 HPV+ and 33,841 HPV- patients. The proportion of HPV+ patients who drink alcohol was 66.05 [95%CI 52.55-78.34] and the proportion of HPV- patients who drink alcohol was 54.8 [95%CI 36.32-72.55] with a difference of 6.76% [95%CI 0.91-12.45; p=0.024. The proportion of HPV+ patients who are married was 59.56 [95%CI 29.19-86.35] and the proportion of HPV- patients who are married was 47.7 [95%CI 22.76-73.34] with a difference of 11.82% [95%CI 5.811-17.73; p=0.0001). The proportion of HPV+ patients who engage in oral-genital sex was 79.9 [95%CI 42.28-99.55] and the proportion of HPV- patients was 50.50 [95%CI 19.91-80.88] with a difference of 29.41% [95%CI 22.5-35.7; p<0.0001). Alcohol use (OR 1.63 [CI 0.90-2.95]; p=0.0032) and a Charlson-Deyo Index of 0 (OR 1.40 [CI 0.95-2.06]; p=0.0069) are associated with HPV+ HNC. Oral-genital sex is also associated with HPV+ HNC (OR 5.21 [CI 1.98-13.73]; p=0.0355). Marital status is not associated with HPV+ cancer (OR 1.47 [CI 1.10-1.98]; p=0.53).

Conclusions: Less commonly assessed factors including the Charlson-Deyo Index, engaging in oral-genital sex, and alcohol use are associated with the development of HPV+ HNC. Marital status is not significantly associated with HPV+ HNC. This type of head and neck cancer can be prevented by the administration of the HPV vaccine, yet the prevalence of HPV+ HNC continues to increase globally. Determining all sociodemographic risk factors can help identify patient populations that will benefit most from public health mitigation efforts including education, vaccination, and screening for early detection.

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#4830

Argentine consortium for the study of HPV in head and neck cancers: HPV genotyping and P16INK4A staining

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Head and neck cancers constitute a serious health problem, not only due to their aggressiveness, but also due to the anatomical complexity of the cervical-facial region, which usually generates serious functional and aesthetic sequelae. Human papillomavirus (HPV) infection has been associated with a proportion of head and neck squamous cell carcinoma (HNSCC), particularly of the oropharynx. In Argentina, there is little information on this topic, so this study was designed to investigate the association of HPV with HNSCC in samples provided by the Argentine Consortium for the Study of HPV in HNSCC.

Methods: A multicentric, descriptive, cross-sectional and retrospective study was carried out on 759 formalin fixed paraffin embedded (FFPE) tissues with histological diagnosis of squamous cell carcinoma from oropharynx (N= 161), oral cavity (N=262), larynx (N=319) and sinonasal tract (N=17). HPV detection and genotyping was done using BSGp5+/6+ PCR combine with reverse hybridization to identify 36 genotypes of high (HR-) and low (LR-) risk HPV. In the HPV-positive samples, the overexpression of the cellular protein p16INK4a was investigated by immunohistochemistry.

Results: A total of 659 FFPE were ß-globin positive and therefore, suitable for HPV analysis. HPV was detected in 20.3% (134/659) of HNSSC samples, encompassing: oropharynx 50% (75/150); oral cavity 12.9% (28/217); larynx 9.03% (25/277) and sinonasal tract 40% (6/15). HPV16 was the most frequent genotype [74.6% (100/134)], regardless of the anatomical sublocation: oropharynx (81.3%), oral cavity (53.4%), larynx (80.0%), and sinonasal tract (66.7%). p16INK4a overexpression was observed in 61.2% (82/134) of HPV-positive cases (almost all cases with a HR-HPV); among them the highest positivity for p16INK4a was observed in oropharyngeal samples (78.7%).

Conclusions: This work provides the first data about HPV types frequency in HNSCC samples from Argentina. The presence of HR-HPV associated with the overexpression of p16INK4a observed could be in favor to a possible etiological association of these viruses (especially HPV16) with the lesion. The establishment of a consortium facilitated access to a large number of samples and demonstrated the richness of multidisciplinary work.

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#4809

The Lack of Standardized Outcomes for Surgical Salvage of Human Papillomavirus (HPV) Positive Recurrent Oropharyngeal Squamous Cell Carcinoma: A Systematic Scoping Review

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is increasing in incidence and while primary treatments are often successful in disease eradication, salvage surgery (SS) remains an important treatment for those patients with recurrent disease. SS for recurrent OPSCC is often the only curative treatment option but has been associated with poor 5-year survival. The impact of HPV status on SS outcomes is unknown. Given the impact of this surgery on patient outcomes and quality of life, it is crucial to understand how SS affects survival endpoints. Current studies provide limited and inconsistent data on this topic.

Methods: Three databases (PubMed, SCOPUS, and CINAHL) were searched for articles published in English that examined adults (>18 years) diagnosed with HPV-positive OPSCC and managed with SS to assess survival endpoints. Two independent authors (ANT and SRS) conducted literature screening, data extraction, and risk of bias assessment using The Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) assessment tool.

Results: The authors screened 1868 articles and 20 articles were included. Appraisal of studies revealed an overall risk of bias, with potential sources related to bias in selection of participants and bias due to confounding. A total of 3,533 HPV-positive OPSCC patients were analyzed. Of these patients, 290 were treated with SS alone and 66 were treated with SS plusadjuvant therapy. Besides one, none of the included articles provided survival endpoints such as Overall Survival (OS), Disease-Free Survival (DFS), or Cancer-Specific Survival (CSS) that were specific to surgically salvaged patients. Instead, studies commonly reported survival endpoints for recurrent disease altogether, not stratified by specific salvage treatments. These parameters were inconsistently reported amongst the studies with only 5 studies reporting 2-year OS, 2 stating 5-year OS, and 2 recording DFS. CSS was reported once. Of the 20 included studies, 14 studies did not report survival endpoints for HPV+ recurrent disease.

Conclusions: Surgical salvage is a treatment option for some cases of recurrent OPSCC. Our goal was to analyze how SS affects patient survival parameters in locoregional and metastatic HPV-positive OPSCC relapse. In the absence of survival-specific data on SS, it is not possible to assess the potential advantages and disadvantages of SS in this patient population. The findings of this scoping review indicate the need for further assessment of survival outcomes of SS specifically, not grouped with other forms of salvage therapy.

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#5458

Colposcopic magnified scanning laser vaporization (CMSLV) for genital warts during pregnancy: a prospective descriptive evaluation of safety and reliability in a Maternal Care Hospital

32 - Genital warts

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Background/Objectives: Genital warts caused by infection with low risk HPV may infect newborns risking to develop Juvenile onset recurrent respiratory papillomatosis (JORRP). No clear guidelines are available to manage genital warts in pregnancy. Although cesarean section is not recommended, almost 20% of warty pregnant patients still undergo cesarean section due to genital warts in labour. Aim was to show efficiency of a minimally invasive laser technique to treat warts in pregnancy.

Methods: A prospective taking care study on all patients diagnosed from 2014 to 2019 with genital warts during pregnancy and submitted to colposcopic magnified scanning laser vaporization(CMSLV)was conducted.Only patients that were followed and delivered at Authors' obstetrical ward were enrolled. All vaporization procedures were performed with a SmartXide2 scanning aided CO2 laser (DEKA M.E.L.A.Srl) at 15 watt of power using an exagonal shape microscan connected to a colposcope by a micromanipulator and tailored on warts'dimension. Procedures were performed applying topical anesthetic agent (lidocaine/prilocaine 5%). Local injectable anesthetic was limited to not-responding pain and wide procedures (1:200000 optocain with adrenaline). The aim of every laser session was no residual disease. Patients were submitted to colposcopy every three weeks until delivery to assess and treat eventual relapse. Laser outcome was evaluated in term of number of treatments per pregnancy. Rates of preterm labour, cesarean section and indication to cesarean section, performed episiotomy, occurred perineal tears were collected and compared to rates of the obstetrical population delivering at Authors' clinic (AOUC) in 2021. Rate of breastfeeding was collected as index of mothers' wellbeing. Infants were followed for three years after birth at neonatologic unit to check for JORRP. Results were statistically analyzed by Chi Square test with Yates' correction considering a $p<0,05$ as significant.

Results: 221 pregnant women were enrolled: 29,8 % needed multiple-site laser vaporization, 70,2% only vulvar procedures; 86% needed a singular procedure, while 14% multiple treatments. 8,1% cesaran section were performed but only 0,9% because of genital warts. No statistically difference in term of obstetrical outcomes were observed among patients who underwent single or multiple procedures (Tab. 1). CMSLV didn't represent a major risk factor for cesarean section or operative procedures when compared to a third level care unit population risk factors (Tab.2). CMSLV treated women seemed to be protected from the risk of perineal tearing probably because of extensive care reserved to genital tissues during labour by midwives aware of the treatment. 78,3% of newborns were exclusively breastfed. No cases of JORRP were registered among the infants.

Conclusions: In contrast with litterature CMSLV minimizes vaporized areas allowing the outpatient simultaneous treatment of multiple genital warts with local anesthesia up to the term of gestation. It reduces the risk of chosing cesarean section as JORRP preventing option under 1% and preserves obstetrical outcomes and mothers'wellbeing.

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#4723

Economic burden of genital warts in Finland in 2018.

32 - Genital warts

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Background/Objectives: Genital warts (GW) represent benign, anogenital epithelial changes occurring in both sexes. 90% of the GWs are caused by human papillomavirus (HPV) types 6 and 11. GWs represent one of the most common sexually transmitted infections peaking in 20-24-year-olds. Majority of the cases are diagnosed and treated in primary care in Finland. Several cycles of pharmacological or physician-performed treatments are usually needed for optimal treatment result, thus leading to high individual and healthcare burden. Current treatments do not destroy the virus itself, and thus the recurrences are common. The main pharmacological treatments of GWs in Finland are imiquimod and podophyllotoxin. In recent years, podophyllotoxin has been irregularly available and on temporary special permit without reimbursement. In 2018 podophyllotoxin was partly reimbursed. Currently, podophyllotoxin is not reimbursed resulting in increased cost for the patient. According to previous estimates, there were on average 6 800 new, incident GW cases annually in 2000-2014. Respective annual costs were on average 2 M€. Non-reimbursed medications were not included in this report (1,2). The objective of this study was to evaluate the prevalence and economic burden of GWs in Finland in 2018 using data from several Finnish national registers.

Methods: A retrospective, cross-sectional multi-registry study estimated the prevalence of GW, the burden of disease and the costs to healthcare based on data sourced from National Finnish registers (year 2018, Suppl File, Figure 1.). GW cases were identified based on GW-specific diagnoses and drug purchases. Primary care and specialized medical care contacts, reimbursed procedures performed by private health care, and drug purchases were collected.

Results: A total of 11 919 unique, prevalent GW cases were treated in Finland in 2018. More than half of the cases lacked public healthcare contacts recorded for GW. The estimated cost of GW treatment for the identified cases was €2.7 million per year, with an average cost per patient of €230. The cost estimation is likely an underestimate due to potentially missing records in the primary care register and podophyllotoxin being currently available only on special permit, making the cost of treatment higher for the patient than it was in 2018. Using the 2018 data, assuming no change in GW-related healthcare resource utilization, the cost in 2021 would have been approximately €3.5 million.

Conclusions: The annual economic burden of GWs estimated in this study in 2018 is almost 35% higher than previously estimated in Finland (€2.7 and €2 million, respectively). The HPV vaccine protecting against GW is currently not included in the gender-neutral national vaccination program. These results should be considered in the evaluation and management of the burden of GWs in Finland.

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Supplementary File, Figure 1.

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#4522

Persistence and recurrence of CIN after LLETZ, with surgical pathological anatomology containing compromised margins, in a Brazilian university hospital service.

35 - Conventional therapies

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Background/Objectives: To assess risk factors for positive margins after large loop excision of transformation zone (LLETZ), persistence and recurrence of intraepithelial lesions in patients undergoing EZT during the study period, and describe clinical characteristics os this popularion.

Methods: We carried out a retrospective cohort study at the Gynecology outpatient clinic of the Federal University of São Paulo, from January 2017 to June 2020. Data collection was carried out through an electronic medical record search, evaluating the follow-up of all patients whose anatomopathological result showed precursor intraepithelial lesion.

Results: Of the 377 patients who underwent EZT in the period, 199 were included in the analysis comprising eligibility criteria. 59.3% of the EZT performed had a length less than or equal to 1.0 cm (excision type 1) and 44.2% had any positive margin, with positive endocervical margin in 19.1% of the cases. Persistence rate of cervical intraepithelial neoplasia was 18.1% and the recurrence rate was 4.5%, showing a significant increase in the risk of lesion persistence in the presence of any compromised margin, and higher risk when the endocervical or radial positive margins when compared to the ectocervical margin. Clinical characteristics as smoking, age or perimenopausal status did not increased reccourence risk.

Conclusions: Excision type was correlated with an increased risk of compromised endocervical margin and positive endocervical and radial margins considerably increased the risk of lesion persistence after EZT.

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#4916

Home-based self-sampling of first-void urine for HR-HPV testing in the casus study: attitudes and preferences from a Belgian colposcopy referral population

37 - Advocacy, acceptability and psychology

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Background/Objectives: Cervical cancer (CC) is the fourth most common cancer globally in women with 99% of cases caused by oncogenic infections with high-risk human papillomavirus (hr-HPV) strains. Women with socio-economical disadvantages and lower education are often underscreened and hard-to-reach leading to an increased risk of developing CC. Successful CC screening programs strongly depend on the participation of the target population. Various barriers are known to contribute to lower participation such as physical discomfort, poor access to health services and lack of knowledge. The CASUS study (NCT04530201, Belgium) aimed at developing a complete CC screening solution based on first-void urine (FVU) self-sampling. Here we report usability attitudes and preferences from women that participated in the CASUS study using FVU as a liquid biopsy.

Methods: Women self-collected FVU samples at home the day prior to colposcopy using the Colli-Pee® Small Volumes containing UCM (N00327) device (Novosanis, Belgium) prefilled with UCM preservative. Afterwards, women completed a questionnaire indicating their usability attitudes and preferences feedback of the Colli‑Pee® Small Volumes urine self-sampler. A specific Systems Usability Scale (SUS) score was incorporated in the questionnaires. A SUS score greater than 68 is considered above average and a SUS score greater than 80.3 indicates that the device is user-friendly and will be recommended by users. Data are presented as relative percentages and as mean ± SEM.

Results: A total of 332 women (26-70y) were enrolled and consented their participation in the CASUS study of which 211 women completed the questionnaire. Overall, 67% of women indicated to prefer FVU self‑sampling over a physician taken PAP smear (33%) for their next CC screening. Additionally, 79% of women indicated to prefer the use of Colli-Pee® Small Volumes over a urine cup (21%) whereby 97% of women experienced Colli-Pee® Small Volumes as easy to use and 98% would use the device again. A total of 210 valid SUS scores were received with an average of 86.19 ± 1.03.

Conclusions: The results of this study show that the majority of women would prefer to self-collect a urine sample at home over a physician-taken PAP smear for their next CC screening. Moreover, Colli-Pee® Small Volumes was considered an easy-to-use and well-accepted self-sampling device for CC screening in a Belgian colposcopy referral population. From a future perspective, these results highlight the possibility of home‑based urine self-sampling as a liquid biopsy in CC screening where underscreened populations could be approached more easily.

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#4981

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38 - Health education

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Background/Objectives: The Cellular and Molecular Cytopathology Training School (CMCTS) provides training events in Cervical Cytopathology, Histopathology and Molecular Pathology in the area of cervical cancer and cervical screening. The CMCTS is supported by CervicalCheck and the Irish Faculty of Pathology.

Methods: The annual activity reports of the CMCTS and CPD event registers from April 2017- October 2023 were reviewed and activity type and the disciplines of attendees were recorded.

Results: To date >126 people have been trained in the CMCTS since April 2017. The CMCTS provided training to Specialist Registrars in Pathology/Pathologists (N=8), Biomedical Scientists (N=29), Colposcopy Specialists in Training (N=32), Colposcopy Specialist Nurses (N=15) and Undergraduates (N=22), Research Fellows (N=4), Laboratory Aides (N=6), Transition Year Students (N=10) and groups of Biomedical Scientists (numerous events and attendances), through a variety of individual sessions, microscopy workshops, lectures, guest lectures, departmental CPD and student placements. The CMCTS also provides research supervision in its state-of-the art Molecular Pathology Laboratory to BSc, MD, MSc and PhD students of Trinity College Dublin and TU Dublin in the areas of cervical screening and molecular epidemiology through the Irish Cervical Screening Research Consortium's research programmes (CERVIVA). In March 2020, the School launched a collaborative QQI Level 9 CPD Certificate Programme with the School of Biological and Health Sciences, TU Dublin, supported by CervicalCheck, aimed at upskilling cervical cytologists in Molecular Cytopathology. This course is the first of its kind nationally and provides the cytologist with the knowledge and understanding of molecular advances in cervical cytopathology.

Conclusions: The CMCTS is a framework for the dissemination of health services research knowledge and insights gained through CERVIVA, directly to health service professionals involved in cervical screening. The CMCTS has an important role to in the development of scientific capacity and expertise for the Irish cervical screening programme (CervicalCheck), particularly in the context of the new National Cervical Screening Laboratory.

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South Africa

Adams Robyn Anne
South Africa

#4509

Visual inspection using naked eye and colposcopy as predictor of high-grade lesions on final histology in HIV-positive and negative south African women

39 - Low resource settings

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Background/Objectives: Although potentially preventable, cervical cancer is the fourth most common cancer among women globally and a leading cause of cancer-related deaths. Women living in resource-limited countries are especially at risk due to poor access to cervical cancer screening and treatment. Alternative cervical cancer screening methodologies have been investigated where cytology-based screening is not feasible. This study aimed to assess the test performance of naked eye visual inspection analysis, in addition to the comparative performance of physician/ colposcopist clinical impression to the RCI grading system for histopathology, in the South African setting.

Methods: WLWH and HIV negative women aged 25 to 65 were recruited from three sites in South Africa.A cross-sectional study which assessed VIA, VILI, colposcopic impression and RCI for the detection of histologically confirmed CIN2+ and CIN3+ was performed. Test positivity rates, sensitivity, specificity, and predictive values were calculated. WLWH and HIV negative women aged 25 to 65 were recruited from three sites in South Africa.A cross-sectional study which assessed VIA, VILI, colposcopic impression and RCI for the detection of histologically confirmed CIN2+ and CIN3+ was performed. Test positivity rates, sensitivity, specificity, and predictive values were calculated.

Results: 344 WLWH and 409 HIV negative women, with a median age of 40 years were included in this analysis. 38.51% of women had a histologically confirmed CIN2+ and 18.99% CIN3+. Overall, positive test rates for VIA were 42.76%; VILI, 45.68%; colposcopic impression, 48.26% and RCI, 46.65%. Overall sensitivities/specificities for VIA and VILI for CIN3+ were 76.92%/65.25% and 75.52%/61.31%, respectively. The sensitivities however increased for WLWH (VIA, 82.61%; VILI, 80.43%) and decreased in HIV negative women (VIA, 66.67%; VILI, 66.67%). Colposcopic impression/RCI performed better in WLWH (PPV, 37.96%/37.74%) than in HIV negative women (PPV, 25.63%/26.80%).

Conclusions: The current study demonstrates that visual inspection methods performs better in WLWH than in HIV negative women. VIA and VILI performed similarly within each sub-population, as did colposcopic impression and RCI. The use of visual inspection methods in cervical cancer screening in WLWH is warranted.

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Canedo Juan
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#5054

Reducing provider perceived barriers to HPV vaccination through a practice facilitation intervention

40 - Public health

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Background/Objectives: HPV vaccine coverage has lagged behind that of other adolescent vaccines (meningococcal and Tdap) in the United States. Provider recommendation is consistently the strongest predictor of HPV vaccine uptake. Practice facilitation is an evidence-based implementation strategy to improve provider adherence to clinical guidelines through provision of training, technical support, and resources to conduct quality improvement. However, little research has applied practice facilitation to HPV vaccination. We compared the impact of coach-based versus web-based practice facilitation on reducing pediatric provider's perceived barriers to HPV vaccine uptake.

Methods: Twenty-one (N=21) community-based pediatric practices in Tennessee, USA, participated in the implementation trial and were randomized to coach-based or web-based practice facilitation arms. Each practice selected four changes to work on during 12-month quality improvement projects, with data feedback reports and support from either periodic coach visits or a web-based resource portal. Providers at study practices were invited to complete a survey at study initiation and at 14-month follow-up. Baseline and follow-up surveys were completed by 93 providers. The survey included 10 items that asked providers' perceptions of barriers to successfully immunizing their patients with HPV vaccine, each with a 4-point Likert scale from 1=Not at All to 4=A Major Barriers. Analyses compared changes in perceptions from baseline to follow up within and across study arms.

Results: Among the providers, 71% were female; 70% were physicians, 28% nurse practitioners, and 2% physician assistants. The largest barriers perceived by providers were: Infrequent office visits made by adolescent patients (Mean=2.5, SD=0.88), HPV vaccine not being required for school attendance (Mean=2.4, SD=0.904), and concern about parents' negative perceptions about the HPV vaccine (Mean=2.3, SD=0.901).Two perceived barriers declined in both study arms ($p<0.05$): provider knowledge about HPV and the HPV vaccine, and provider concern about parents' negative perceptions about the HPV vaccine. Providers in the Coach-Based arm only reported a decrease in the barrier of personal concerns about HPV vaccine safety ($p<0.05$). Providers in the Web-Based arm only showed a decrease in the barrier of personal discomfort talking about sexually transmitted infections with parents and patients ($p<0.05$).

Conclusions: While the perception of external barriers did not change, practice facilitation in both delivery formats led to reductions in several perceived barriers related to knowledge and attitudes. Future research should examine correlations between reducing provider-perceived barriers and increases in HPV vaccine uptake.

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#4922

Cervical cancer risk factors and symptoms awareness in hard-to-reach populations in Bangladesh, India, Slovakia and Uganda

40 - Public health

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Background/Objectives: Cervical cancer continues to disproportionately affect vulnerable populations and hard-to-reach areas, particularly in low- and middle-income countries. Succesful implementation of cervical cancer screening programs requires consideration of factors related to acceptability and uptake rates of screening. In this context, awareness of cervical cancer and its risk factors and symptoms can be important indicators to take into account. As part of the PREvention and SCReening Innovation Project Toward Elimination of Cervical Cancer (PRESCRIP-TEC), we aimed to study awareness of cervical cancer among target populations in Bangladesh, India, Slovakia and Uganda.

Methods: We conducted a survey in four countries using an adapted version of the African Woman Awareness of CANcer (AWACAN) instrument, originally developed for measuring awareness of breast and cervical cancer. We included questions on cervical cancer and developed an additional version for male / household decision-maker respondents. The instrument was piloted in participating countries to adjust for cultural factors and appropriateness. Using the original instrument's scoring methods, scores of knowledge of risk factors and symptoms were compiled (maximum score = 11).

Results: A total of 5906 respondents were surveyed (63% female). Average age of female participants (including female household decision-makers) ranged from 51.0 in Bangladesh to 35.8 in Slovakia. Mean cumulative scores for knowledge of risk factors among female respondents (potential participants of the screening program, excluding household decision-makers) were 4.4 (SD 3.6) in Bangladesh, 3.0 (SD 2.6) in India, 5.1 (SD 2.5) in Slovakia and 7.4 (SD 3.3) in Uganda, while the scores for knowledge of symptoms were 6.9 (SD 3.8) in Bangladesh, 3.0 (SD 3.4) in India, 5.0 (SD 3.4) in Slovakia and 7.1 (SD 3.4) in Uganda. Male/household decision-maker respondents in India demonstrated higher levels of knowledge of risk factors and symptoms compared to female respondents on average (3.73 vs 3.0 and 4.16 vs 3.0), which did not appear to be the case in the other countries' study populations.

Conclusions: We observed considerable variation in awareness of cervical cancer, its symptoms and risk factors across diverse settings. Communication efforts to enhance the implementation of screening in these areas should account for context-specific gaps in knowledge and awareness. There may be a need for further exploration of awareness differences between household decision-makers and potential screening program participants.

Stefanos Ruth
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#4836

Declines in vaccine-type human papillomavirus prevalence IN U.S. females across racial/ethnic groups: national health and nutrition examination survey

40 - Public health

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Background/Objectives: HPV vaccination was included in the U.S. national immunization program in 2006. Quadrivalent HPV vaccine (4vHPV) was mainly used through 2015; after the end of 2016, only 9-valent HPV vaccine (9vHPV) was available. Routine vaccination is recommended at age 11-12 years with catchup through age 26. To evaluate equity of vaccine impact, we determined vaccine-type HPV prevalence in the nationally representative National Health and Nutrition Examination Survey (NHANES) in 2003-2006 (prevaccine era) and 2015-2018 among females, overall and by race/ethnicity.

Methods: We analyzed HPV DNA prevalence in self-collected cervicovaginal specimens, demographic characteristics and sexual behavior data from females aged 14-34 years. We compared vaccine era to prevaccine 4vHPV-type (6,11,16,18), 5-additional 9vHPV-type (31,33,45,52,58), and non-9vHPV-type prevalences, using prevalence ratios (PR) and 95% confidence intervals (CI) among sexually experienced females, overall and for non-Hispanic White (NHW), non-Hispanic Black (NHB) and Mexican American (MA) females.

Results: In 2015-2018 compared with the prevaccine era, among 14-19-year-olds, 4vHPV-type prevalence decreased from 19.3% (15.6-23.8) to 1.5% (0.5-4.2), PR=0.08 (0.03-0.22); NHW 20.3% (14.9-27.0) to 1.9% (0.4-8.4), PR=0.09 (0.02-0.43); NHB 22.8% (17.3-29.4) to 3.9% (1.5-10.1), PR=0.17 (0.06-0.46); MA 16.4% (10.8-24.0) to 0%, PR not defined (Table). Significant declines in the 5 additional 9vHPV-types were also observed among MA 14-19-year-olds. In 20-24-year-olds, 4vHPV-type prevalence decreased from 17.9% (13.8-22.8) to 3.5% (1.7-7.0), PR=0.20 (0.10-0.40); NHW 20.0% (14.9-26.3) to 4.4% (1.8-10.2), PR=0.22 (0.09-0.53); NHB 20.3% (12.1-32.1) to 2.4% (0.6-9.1); PR=0.12 (0.03-0.49); MA 8.5% (3.0-22.2) to 0%, PR not defined. No significant declines in 4vHPV types or additional 9vHPV types were observed in 25-29- or 30-34-year-olds.

Conclusions: Within 12 years of vaccine introduction, large declines in 4vHPV-type prevalence have been observed among 14-24-year-old sexually experienced NHW, NHB and MA females. Racial/ethnic equity of 9vHPV impact can be evaluated through future NHANES monitoring.

Eurogin_2023_NHANES_Table

Chow Eric
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#4811

Accuracy of self-reported human papillomavirus vaccine using computer-assisted self-interview in young men who have sex with men

40 - Public health

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Background/Objectives: Gay, bisexual, and other men who have sex with men (MSM) are at a higher risk of acquiring human papillomavirus (HPV). In 2017-2019, a time-limited HPV catch-up program was implemented for MSM aged≤26 years in Victoria, Australia. This study aimed to examine the accuracy of computer-assisted self-interviewer to collect HPV vaccination status among young MSM who were eligible for the HPV catch-up program.

Methods: We conducted a retrospective observational study of young MSM aged 23-30 years attending MelbourneSexual Health Centre (MSHC), Australia, in 2020-2021. This age cohort was selected because they were eligible for the HPV catch-up program but missed the school-based HPV program. Individuals were asked to self-report their HPV vaccination status (vaccinated, unvaccinated, unsure) using computer-assisted self-interviews. The primary outcome was the sensitivity and specificity of self-reported HPV vaccination status.

Results: We identified 1,786 eligible men who attended MSHC in 2020-2021 and also had at least one clinic visit in2017-2019. The median age was 27 (IQR=25-28) and half (49.4%, n=883) were born in Australia. There were1,665 men who self-reported HPV vaccination status (48.8% [n=812] vaccinated, 17.4% [n=289] unvaccinated,33.9% [n=564] unsure), and 1,159 men had had HPV vaccine administered at MSHC. The median time since the last HPV vaccine was 1.7 (IQR=1.1-2.3) years. Classifying men with unclear vaccine status as unvaccinated, self-reported HPV vaccination had a sensitivity of 61.3% (95% CI 58.9%-63.6%; 661/1079), a specificity of 74.2%(95% CI 72.1%-76.3%; 435/586), a positive predictive value of 81.4% (95% CI 79.5%-83.3%; 661/812), and a negative predictive value of 51.0% (95% CI 48.6%-53.4%; 435/853).

Conclusions: The sensitivity of self-report HPV vaccination status was low among young MSM and one-third were unsure about their HPV vaccination status. A registry that collects vaccination records and provides access to healthcare providers would be useful to clinical recommendations.

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#4768

Evaluation of the impact of the new school-entry policy on HPV vaccination in PR

40 - Public health

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Background/Objectives: In August 2018,PR became the 5th state or territory in the Unites States of America to adopt an HPV vaccine school-entry policy, requiring it for 6th graders starting in August 2018.While school-entry requirements are generally accepted as an effective approach for increasing vaccination rates, there are few studies that have documented their impact on improving this primary prevention strategy. The objective of this study was to evaluate the impact of the HPV school-entry policy in PR on HPV vaccine coverage.

Methods: A pre-post natural experiment was used. The study population included adolescents registered in the PR Immunization Registry during 2017-2019. We calculated HPV vaccine initiation and up-to-date (UTD) vaccine coverage rates among adolescents aged 11-12 years old.

Results: During the study period, vaccine data corresponding to a total of 495,327 adolescents (50.9% male and 49.1% females) were included for analysis. After policy implementation, a marked increase in HPV vaccine initiation among 11- to 12-year-old adolescents was observed across years 2017 (a pre-policy year), 2018, and 2019 (58.3%, 76.3%, and 89.8%, respectively). UTD coverage also showed a moderate increase after policy implementation among 11- to 12-year-old adolescents. The gap between sex groups in vaccine initiation and UTD coverage narrowed; from 19% reduction in vaccine initiation and 7% increase in UTD vaccine (both significant at $p<0.05$).

Conclusions: This study demonstrated evidence of improvement in HPV vaccination initiation and UTD vaccine coverage rates following implementation of the school-entry policy and a narrowed sex gap in vaccine rates over time in PR. Future analyses should assess how the policy continues to affect vaccine coverage in subsequent years and how the COVID-19 pandemic has impacted HPV vaccination uptake.

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#4491

Viral whole-genome sequencing reveals high variations in APOBEC3-editing between HPV risk categories

02 - Viral and molecular biology

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Background/Objectives: Human papillomavirus (HPVs) are responsible for cervical cancer. The enzymatic activity of APOBEC proteins, a family of cytidine deaminases, contributes to the innate immune response to some viruses including HPV. The role of APOBEC-induced mutations in HPV-driven carcinogenesis has recently gained increasing attention. However, little is known about differences among HPV types regarding genetic diversity and APOBEC3-induced mutations between risk categories (low- and high-risk HPVs). The role of APOBEC3-induced mutations in HPV-driven carcinogenesis is discussed and whether they could contribute to the carcinogenic potential of some HPV types more than others is yet to be explored.

Methods: Using a capture-based next-generation sequencing, 156 HPV whole-genome sequences covering 43 HPV types were produced from paired cervical and anal swabs of 30 Togolese female sex workers sampled in 2017. Genetic diversity and APOBEC3-induced mutations rates were investigated at both viral whole-genome and gene levels. APOBEC3-induced mutations were identified as C>T mutations in the TCW nucleotide context (W being either A or T). Genomes or genes were considered edited by APOBEC3 when the RatioC>T between C>T mutations in all TCW motifs and C>T mutations in any other context was above 2.

Results: High variations in genetic diversity among HPV types were observed. The E6 gene was lowly conserved in low-risk HPVs (lrHPVs), in contrast to high-risk HPVs (hrHPVs) (p=0·009). APOBEC3-induced mutations were found to be more common in lrHPVs than in hrHPVs (p=0·005) (Fig 1A). To generalize these observations, we conducted a similar analysis using a large sequence dataset containing the most prevalent lrHPVs (HPV6 and HPV11, n=375) and hrHPVs (HPV16 and HPV18, n=777) types retrieved from the GenBank database. By performing 100 replicates corresponding to a random draw of 50 sequences, equally distributed, we observed that HPV6 and HPV11 significantly accumulated more APOBEC3-induced mutations than HPV16 and HPV18 (Fig 1B). APOBEC3-induced mutations were highly found in E4 and E6 genes for lrHPVs 6 and 11, with a RatioC>T > 2 in 91.9% and in 72·6% of the sequences, respectively, but were almost absent in hrHPVs 16 and 18 (Fig 1C).

Conclusions: Our findings unraveled striking genetic differences between lrHPVs and hrHPVs. Overall, low-risk HPVs accumulated APOBEC3-induced mutations at a higher rate compared to high-risk HPVs. These various rates of APOBEC3-induced mutations could contribute to different oncogenic potentials between HPV types and risk categories.

Figure 1

López-codony Victoria
Spain

López-codony Victòria
Spain

#4979

HPV genotyping using ALLPLEXTM HPV HR detection in paired physician- (THINPREP® liquid-based cytology) and self-collected (EVALYN brush) vagino-cervical specimens

09 - HPV testing

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Background/Objectives: Human Papillomavirus (HPV)-based cervical screening is replacing cytology-based, which in turn, facilitates the introduction of self-collection protocols. Recent studies have shown that the PCR Ct value could be used alongside other factors, such as HPV individual genotype, to identify women with a higher risk of progression. Here, we analyse the HPV testing results obtained with the new AllplexTM HPV HR Detection assay (Seegene) in a set of paired physician- and self-collected vagino-cervical specimens. Results were compared with previously obtained data using the COBAS 4800 HPV assay.

Methods: AllplexTM HPV HR Detection is a real-time PCR-assay, which amplifies specific targets for 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and provides and individual CT value for each target. A total of 286 paired specimens (143 self-collected vaginal specimens using the Evalyn brush and 143 Thinprep® liquid-based cytology specimens collected by physicians), which had been previously tested with COBAS® 4800 HPV, were analysed using the AllplexTM HPV HR Detection assay. For each batch of 92 samples, acid nucleic extraction (2h 13min) and PCR set up (22min) was performed in a STARlet station using the STARMag 96 X 4 Universal Cartridge Kit and the AllplexTM HPV HR Detection kit. The PCR run was performed in a CFX96TM real-time system (1h and 43 min). Results were analysed using Seegene Viewer V3 software and samples were classified according to the positivity for each HPV target (Figure 1).

Results: Using as reference the set of physician-collected specimens, 40 women (27.9%) were HR-HPV positive. HPV16 (20%) followed by HPV56 (17.5%) and HPV66 (17.5%) were the most frequently detected genotypes. Nine women (6.3%) showed a multiple infection. Ct values for HPV16, HPV56 and HPV66 range from 30.8 to 39.8, 32.7 to 41.4 and 29.9 to 40, respectively. The overall percent agreement (OPA), the positive percent agreement (PPA) and the negative percent agreement (NPA) between AllplexTM HPV HR and COBAS® 4800 HPV, using Thinprep® specimens, was 96.5%, 88.9% and 100%, respectively (Table 1). For the detection of HPV16, HPV18 or other HR-HPV, OPA was 98.6%, 100% and 95.1%, respectively (Table 2). For self-collected samples, OPA, PPA and NPA were 95.8%, 100% and 86.7%, respectively.

Conclusions: AllplexTM HPV HR Detection assay showed a good analytical performance for detecting and genotyping the HR-HPV types when compared to COBAS® 4800 HPV assay results. However, further studies using the international HPV guidelines defined by Meijer and VALGENT consortium are needed to confirm the clinical validation of AllplexTM HPV HR Detection and to evaluate the clinical significance of the Ct values obtained for each genotype.

Mino (rista) Mirela
Albania

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#5813

High-risk HPV infection in Albanian women and some factors associated with it

10 - HPV screening

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Background/Objectives: The high-risk HPV infection is considered the most important factor for the development of cervical cancer. The high risk HPV screening tests, as part of the routine examinations and women who have come out positive, perform a diagnostic colposcopy by a qualified gynecologist and, when necessary a biopsy is performed. A multitude of risk factors favor HPV infection. This study was conducted to: (1) determine the prevalence and (2) make a comparative analysis of some risk factors of cervical cancer, attitude and practice between rural and urban women of Albania.

Methods: During the month of December 2019 approximately 13900 test kits distributed in health care centers and more than 10002 samples were collected back. These kits are self-sampling. The kits are tested at the National Public Health Institute (NIPH) and afterwards the results are delivered to the local health care centers.

Results: Total high risk HPV prevalence in this sample was 6.2%. HPV prevalence is significantly higher in urban populations of women (8.2%) compared to rural areas (4.7%). This confirms an increased risk for infection within a potentially growing urbanization in the future of Albania. On the other hand, average number of abortions is slightly higher among HPV positives, especially when the categories of women who had 2 and more aborts are compared. Of all HPV positive women, 7.6% of them were also smokers.

Conclusions: We have seen better and more inclusive results with HPV screening to prevent cervical cancer. This is due to self-sampling and easier logistics, only women who have tested positive are followed by a coloposcopy visit. Women of lower socio economic classes and those in rural areas, while have been showing lower HPV infection prevalence, were more inclined to use the national systematic screening program, attracted by easy access and free of cost. The benefit of the organized screening resulted in a further decline in incidence rates. It's necessary to expand the screening program in 35-39 age group, since the age of the first sexual intercourse has been lowered.

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#5797

HOPE5 study: exploring new prognostic biomarkers for HPV-associated oropharyngeal cancer

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oropharyngeal cancers (OPC) etiologically related to HPV infection show better prognosis and response to therapy. Nevertheless, about 20% of HPV-driven OPC do not display these characteristics, highlighting the need for new biomarkers to improve patient stratification. Previously, we have developed a method to detect a specific HPV16-E5 transcript. So far, only few studies have assessed HPV16-E5 expression in OPC, with conflicting results regarding its significance as a prognostic marker. In order to better clarify the role of E5 in the identification of potentially transforming infections, the HOPE5 study aimed at evaluating for the first time HPV16-E5 specific mRNA in HPV-driven OPC patients. Since therapies targeting the Epidermal Growth Factor Receptor (EGFR) have been proposed as de-escalation strategies in HPV-related OPC patients, this biomarker was also evaluated.

Methods: Formalin-fixed, paraffin-embedded (FFPE) tissue samples of HPV16-driven OPC (HPV16-DNA positive/p16 positive) were retrieved from the archives of the Pathology Department of the Regina Elena National Cancer Institute (Rome, Italy). RNA, extracted using the RNeasy kit (QIAGEN), was retro-transcribed (GeneAmp RNA PCR kit Applied Biosystem), and a real time-PCR was performed with 2X Kapa SYBR Fast qPCR Master Mix (KAPA) using E5-specific primers encompassing splicing site (880-3358). Transcripts for HPV16-E6/E7 were also analyzed as previously described (1, 2). EGFR expression was assessed by immunohistochemistry (3C6 primary antibody, Ventana). Oral rinse-and-gargles (ORG) were collected from healthy individuals at ENT outpatient clinics of 5 Italian regions (LILT Provincial Committees), using 15 ml of a commercially available mouthwash. They were tested for HPV-DNA by Xpert HPV (Cepheid).

Results: Overall, 84 HPV16-driven OPC were selected for the HOPE5 study. Preliminary results on 24 OPC showed that E6/E7 transcripts were always detected, as well as polycistronic transcripts containing E5 coding sequence. Differently, E5-specific transcripts were detected in 2/24 (8.3%). Overall, 47 OPC were evaluated for EGFR and 24 (51.1%) showed a positive staining, with the percentage of tumor cells displaying moderate/strong staining ranging from 10% to 90%. In parallel, 31 ORG were collected and 2 (6.4%) were HPV16-DNA positive, but negative for HPV16-E5 mRNA.

Conclusions: Further evaluations are required to assess the possible prognostic role of E5-mRNA and EGFR. Investigation of HPV16-E5 mRNA will be carried out on the remaining HPV16-driven OPC. HLA expression will be also evaluated, and, together with EGFR expression will be correlated with the clinical outcome.

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#4772

Efficacy of the glycyrrhizinic acid in the treatment of low-risk cervical preinvasive lesions

23 - Diagnostic procedures / management

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Background/Objectives: The most common cervical precancerous disease is low-risk intraepithelial neoplasia or CIN 1. Pharmacological treatment with glycyrrhizinic acid could reduce persistent human papillomavirus (HPV) infection, the incidence of CIN 1, and the use of more aggressive therapies. The study aimed to investigate the efficacy of the glycyrrhizinic acid treatment for CIN1 lesions.

Methods: A prospective study was done in Riga East Clinical University Hospital from July 2017 to May 2022. Women with histologically confirmed CIN 1 in cervical biopsies were included in the study. Participants of the study group members used glycyrrhizinic acid spray (Epigen spray) topically for 6 months 10-day per month (Epigen 10-day subgroup) or 20-day per month (Epigen 20-day subgroup). Women in the control group have no treatment. During two follow-up visits six months apart cytological, colposcopic, and histological examination was done. All patients were screened for HPV before enrolment and during the 1st follow-up visit.

Results: There were 50 patients of the Epigen (19 patients in the Epigen 10-day subgroup and 31 patients in the Epigen 20-day subgroup) and 50 patients of the control group involved in the study. At the first follow-up visit, there was no difference in terms of histologically proven persistence or improvement between study and control groups, though progression to CIN 2 was more common in the control group compared to Epigen 20-day subgroup (31.1% vs 6.7%, p=0,03). No such relationship was found during the second follow-up visit. Large loop excision of the transformation zone after the first follow-up visit was also statistically significantly more frequent in the control group, 10% in Epigen 20-day subgroup vs 30% in the control group, p=0,032. No statistically significant difference was found in the incidence of improvement or deterioration between Epigen 10-day use and the control group. The most commonly detected HPV types among the enrolled women were 16, 31, 33, 51, and 56. There was no statistically significant difference in distribution and changes in virus concentration over time between groups.

Conclusions: The vaginal spray of the glycyrrhizinic acid used 20 days per month for six months decreases the risk of the deterioration of CIN 1 lesions. The glycyrrhizinic acid used locally does not affect HPV clearance or decrease in concentration and does not prevent new infections. Multicenter double-blind randomized controlled trials are needed to confirm the findings of this study.

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#4894

RELATION OF HPV-RELATED BIOMARKERS EXPRESSION AND CERVICOVAGINAL INFECTIONS IN WOMEN OF REPRODUCTIVE AGE HARBOURING CERVICAL DYSPLASIAS IN A COLPOSCOPIC POPULATION

34 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Sexually transmitted infections (STIs) represent a major global public health issue. Despite vaccination implementation, anogenital HPV infections are very common and can lead to precancerous lesions and cervical cancer, while robust evidence associates infections caused by Mycoplasma genitalium (Mg), Mycoplasma hominis (Mh), Ureaplasma parvum (Up) and Ureaplasma urealyticum (Uu) with adverse obstetric outcomes such as early miscarriages, increased risk for preterm delivery and bronchopulmonary disease in premature newborns. In addition, Chlamydia trachomatis (Ct), appears to be the leading cause of infertility and pelvic inflammatory disease (PID) in women of reproductive age in the Western world. The present study aims to investigate the expression of HPV-related biomarkers and the co-infection of other sexually transmitted pathogens of the lower genital tract (chlamydial, mycoplasma & ureaplasma infections), in women with cervical intraepithelial lesions (CIN) referred for colposcopic evaluation with biopsies, and their correlation with histological grade.

Methods: All women enrolled in the study had a liquid-based cytology (LBC) smear sample which was examined for cytology, HPV DNA typing as well as common STIs (Ct, Mg, Mh, Up, Uu) using NAATs. All women underwent colposcopically-guided cervical biopsies, while full demographic and sexual history data were recorded.

Results: A total of 53 women have been included in the study so far with the average age of the population being 31.2 years; only 36% having been vaccinated against HPV. Forty-four women (83%) tested positive for HR-HPV while 13.2% of the population tested positive for LR-HPV. All women with cytological HSIL tested positive for HR-HPV, with 88.9.3% (8/9) individuals histologically confirmed as CIN2+ (4 cases CIN2 & 4 cases CIN3). Notable was that 54.7% of the study population tested positive for STIs. Twenty-nine individuals tested positive for Ureaplasma spp (Up & Uu), while multiple infections with other pathogens (Ct, Mh & HSV-1) were present in only 3 women. From the total population, in 37 women (69.8%) the histological report revealed a low-grade lesion (CIN1) and in 14 individuals (26.4%) a high-grade lesion (CIN2+).

Conclusions: Despite STIs can be prevented and treated reliably by anti-HPV vaccination and antibiotic administration, they still represent an important public health issue. The inclusion of STIs screening in the existent one for cervical cancer is a technically feasible strategy for young individuals, which could potentially reduce the risk of long-term complications such as infertility and adverse obstetric outcomes in these populations. The results of this pilot study warrant further investigation.

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#4834

CENTRAL SENSITIZATION IN VULVODYNIA AND ENDOMETRIOSIS: WHAT HAVE WE BEEN OVERLOOKING SO FAR?

27 - Vulvar diseases and neoplasia

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Background/Objectives: Although chronic pain is the most prevalent health condition worldwide and it accounts for the highest number of years lived with disability, both patients and clinicians still find it hard to recognize it as a health condition in its own right. Often, health care providers find it challenging to consider patients as credible reporters of pain and resort to psychogenesis even in the presence of organic etiologic factors. Moreover, women experience more frequent and greater pain than men, although they receive less adequate treatment, also because they are perceived as more anxious than males. Recent clinical research has lead to hypothesize a common etiology for overlapping chronic pain conditions and mood disorders, namely central sensitization (CS), which originates from an alteration of the pain processing pathways in the central nervous system. Vulvodynia and endometriosis are the two gynecological diseases included in the National Institutes of Heath Pain Consortium list of Chronic Overlapping Pain Conditions (COPCs). These are a set of conditions, which often co-occur and appear to share common underlying mechanisms, first of all central sensitization. The aim of this review was to collect all available evidence regarding the potential role of central sensitization in vulvodynia and endometriosis.

Methods: A systematic literature search was performed between July and August 2022 using the electronic database PubMed. The search strategy included terms combined with the Boolean operators "OR" and "NOT"; the final string research was the following: vulvodynia OR vestibulodynia OR endometriosis AND (pain OR hyperalgesia OR nociplastic OR allodynia) AND "central sensitization" NOT (dysmenorrhea). Non-original articles, abstracts, studies performed on animal models and papers not written in English were excluded. Due to the exiguous number of retrieved studies and the heterogeneity in outcome measures, the extracted data was summarized using a narrative approach, rather than a quantitative methodology.

Results: Ten articles were chosen for the review. Participants' mean age was 39.2 years (SD = 5.1). Among serum markers of central sensitization, nitric oxide (NO) levels were greater in women with endometriosis than in controls, while brain-derived neurotrophic factor (BDNF) and S100B levels differed among pain conditions with structural anomalies (i.e endometriosis) and those without. Functional MRI showed different resting state networks between patients with endometriosis and controls. In many of the neurophysiology studies, women with vulvodynia or endometriosis had reduced pain thresholds but normal sensory thresholds, compared to healthy controls. Lastly, self-reported questionnaires suggested a central component of pain in women with endometriosis-related dyspareunia and associated bladder/pelvic floor tenderness, compared to those with endometriosis-related dyspareunia without bladder/pelvic floor tenderness.

Conclusions: The management of vulvodynia and endometriosis may benefit from a new perspective, which considers their possible central etiology. It is compelling that treatment of pain starts to be considered a therapeutic goal in its own right and that women with central sensitization receive multidisciplinary care, including psychotherapy for the treatment of comorbid mood disorders, when present, irrespectively of the fact that these are a cause or a consequence of their pain condition.

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#5888

New concepts of cervical screening and follow-up during the COVID-19 pandemic in China

01 - HPV disease and COVID-19

Background/Objectives: Recent cancer statistics show that the new female cancer cases and the mortality rate are disproportionately high. In many countries, cancer screening programs were paused during the COVID-19 pandemic causing a screening disruption for an unknown period. It is the right time to rethink patients' actual needs and values in screening, repeated follow-up, treatment, and fertility preservation. Therefore, setting an objective, easy-to-interpret, compassionate, and specific cervical cancer screening strategy for reducing contact time with patients is still necessary. The tests are easy operation in a limited time, and the accuracy is better than the previous methodology.

Methods: A prospective study of outpatient opportunistic cervical cancer screening was conducted with multiple centers in China from 2019 to 2020. Twenty thousand participants were recruited for this study, with a one-year follow-up. All enrolled participants were collected cervical exfoliated cells by cervical brush and tested for cytology (LBC), HPV, and dual-gene methylation testing (Beijing Origin Poly Bio-Tec Co., China) and compared with pathological results. Classify groups according to age and further analyze the sensitivity and specificity of different methods.

Results: In the age group of 35 or less, the methylation detection technology showed a lower positive detection rate in the pathology of CIN1 or normal (<8%). In comparison, TCT (ASCUS+) and HPV16/18(+) showed a high positive rate (70%, 40%, respectively). In CIN2 and worse (including CIN3 and Cancer), when the combined detection of methylation technology and HPV16/18 is used, it can significantly improve the shortcomings of the single screening technology. In the aged 50 and above group, methylation can express a lower positive detection rate for CIN1(<15%), while TCT and HPV can represent a higher positive rate (70% and 25%). However, the positive methylation rate at CIN2 & CIN3 is higher than in young women.

Conclusions: This multi-center prospective study explored the application value of dual-gene methylation detection for outpatient opportunistic cervical cancer screening. According to our findings, the dual biomarkers for early cervical cancer have a higher detection rate for squamous cell carcinoma and adenocarcinoma. A negative result to predict the regression of lesions for younger women. This means that the use of methylation testing to assist cervical cancer screening has the potential to be a better application in different age groups.

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#4770

ARTIFICIAL INTELLIGENCE FOR IMAGE-BASED HPV STATUS PREDICTION IN HEAD AND NECK CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Accurate early detection of the human papillomavirus (HPV) status is crucial to identify at-risk populations, stratify head and neck cancer (HNC) patients, personalize treatment options, and predict prognosis. Several studies indicated the association between radiomic features and HPV status. Given artificial intelligence (AI) is an emerging tool to dissect imaging features, this systematic review and meta-analysis aims to evaluate the clinical performance of AI on radiomic image-based HPV status prediction in HNC.

Methods: This systematic review and meta-analysis was performed in accordance with the PRISMA guideline. A systematic literature search was conducted in databases including Ovid-MEDLINE, Embase, and Web of Science Core Collection for studies continuously published in English from inception up to 30th October, 2022. Pertinent studies with synonymous keywords "AI", "HPV", "performance", and "HNC" were included. A mixed effect model was used for meta-analysis synthesis and we mainly reported pooled sensitivity, specificity, area under the curve (AUC), and their 95% confidence intervals (CI) for all studies and studies only reporting the highest performance. Four subgroup analyses were further explored including: (1) validation types; (2) imaging modalities; (3) exclusion of poor images or not; (4) open access data or not. Finally, heterogeneity, the risk of bias and applicability concerns, and publication bias of the included studies were assessed.

Results: Totally, 21 original studies were included in the systematic review, 15 of which were eligible to generate 26 contingency tables for meta-analysis. The pooled sensitivity and specificity for all studies were 0.76 (95% CI: 0.73-0.80) and 0.74 (95% CI: 0.69-0.78) respectively, with an AUC of 0.82 (95% CI: 0.78-0.85). When only including one contingency table reporting the highest performance in each study, the pooled sensitivity and specificity were 0.79 (95% CI: 0.74-0.83) and 0.75 (95% CI: 0.69-0.80) with an AUC of 0.84 (95% CI: 0.80-0.87). Only low and moderate heterogeneities were observed (I2 of sensitivity and specificity were 37.21% and 57.92% respectively).

Conclusions: This evidence-based study shows an acceptable overall performance of AI algorithms to predict HPV status in HNC. This fast and low-cost method might be useful to be further applied in cancer screening or clinical practice. However, both the sensitivity and specificity of AI are relatively low compared to the routine test p16 immunohistochemistry. The exploitation and optimization on AI algorithms warrant further research.