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INNOVATIONS IN HPV RESEARCH AND GLOBAL CANCER SOLUTIONS

AN INTERNATIONAL COLLABORATIVE CONFERENCE

Congress Presidents | **Hans Berkhof (Netherlands) • Miriam Elfström (Sweden)**

ABSTRACTS

MAIN CONGRESS PROGRAM

SS01 - Newest insights into oncogenesis

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#7755

Downregulation of miR-193a/b-3p contributes to anchorage-independent growth in HPV-transformed keratinocytes through PI3K/AKT pathway

25 - Cervical neoplasia

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Background/Objectives: Cervical cancer is caused by a persistent infection with high-risk types of HPV and accumulation of (epi)genetic alterations in the host cell. Acquisition of anchorage-independent growth represents a critical hallmark during HPV-induced carcinogenesis, thereby yielding most valuable biomarkers for early diagnosis and therapeutic targets. In a previous study, we found that miR-193a-3p and miR-193b-3p were involved in anchorage-independent growth. This study aimed to delineate the role of miR-193a/b-3p in HPV-induced carcinogenesis and to identify their target genes related anchorage-independent growth.

Methods: Cell viability and colony formation were assessed in SiHa cancer cells and HPV-16 and -18 immortalized keratinocytes (FK16A/FK18B) upon miR-193a/b-3p overexpression to validate their functional involvement. Online target predicting programs (ENCORI and miRDB) were used to find candidate mRNAs targets of miR-193a/b-3p. mRNA targets were further selected based on publicly available expression dataset. Targets were validated by RT-qPCR, luciferase reporter assays and western blots.

Results: miR-193a-3p and miR-193b-3p largely reduced cell growth of SiHa, FK16A and FK18B in anchorage-independent conditions and showed minor effect in anchorage-dependent conditions. Fifteen genes were identified as potential targets related to anchorage-independence. Seven genes showed reduced mRNA expression upon miR-193a-3p and miR-193b-3p overexpression. A direct interaction was confirmed using luciferase assays for 6 genes: LAMC1, KRAS, PPP2R5C, PTK2, SOS2 and STMN1. Western blot analysis of three targets showed a reduced protien level. Both miR-193a/b-3p are downregulated in high-grade CIN lesions and miR-193b-3p also downregulated in cervical cancers. All 6 targets were overexpressed in cervical cancers and/or high-grade CIN lesions.

Conclusions: miR-193a-3p and miR-193b-3p reduce anchorage-independent growth of HPV-transformed cells through targeting LAMC1, KRAS, PPP2R5C, PTK2, SOS2 and STMN1. Target upregulation in cervical cancer underlines the biological relevance of miR-193a-3p and miR193b-3p downregulation during HPV-induced carcinogenesis.

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Croatia

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#7761

VIRAL-HOST PROTEIN INTERACTIONS PERTURBING CELL PROLIFERATION AND MIGRATION

02 - Viral and molecular biology

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Background/Objectives: While a small proportion of high-risk (HR) alpha (a) human papillomaviruses (HPVs) is associated with numerous human malignancies, of which cervical cancer is the most prevalent, beta (ß) HPVs predominantly act as co-factors in skin carcinogenesis. A characteristic feature of both a- and ß-E6 oncoproteins is the presence of the LXXLL binding motif, which a-E6s utilize to form a complex with E6AP and which enables ß-E6s to interact with MAML1.

Methods: Immunoprecipitation and GST pull-down assays were used to asses viral-host protein interactions. siRNA silencing, immunofluorescence, half-life experiments, cell fractionation, cell proliferation and wound healing/scratch assays were used to investigate biochemical and biological consquences of these interactions.

Results: Here we show that multiple a-E6 oncoproteins bind to MAML1 via the LXXLL binding motif and that this results in increased protein stability. Moreover, ß-E6 oncoprotein stability is also dependent on the interaction with MAML1. Additionally, in the absence of MAML1, endogenous HPV-8 E6 and HPV-18 E6 are rapidly degraded at the proteasome. Ablation of both E6AP and MAML1 leads to an even more profound downregulation of a-E6 protein expression, whereas this is not observed with ß-E6. This highly suggests that there is one cellular pool for most of ß-E6 that interacts solely with MAML1, whereas there are two cellular pools of HR a-E6, one forming a complex with MAML1 and the other interacting with E6AP. Furthermore, MAML1 induces HPV-8 E6 shuttling from the nucleus to the cytosolic fraction, while MAML1 interaction with HR E6 induces a drastic nuclear and membrane upregulation of E6. Interestingly, the HR a-E6/MAML1 complex does not affect targeting of some of the known HR E6 cellular substrates such as p53 and DLG1. However, MAML1 and E6AP joint co- expression with HR a-E6 leads to a significant increase in cellular proliferation, whereas silencing MAML1 decreases wound closure in HeLa cells.

Conclusions: These results demonstrate that HR a-E6 interaction with MAML1 results in a stable form of E6, which likely modulates MAML1's normal cellular activities, one consequence of which being an increased proliferative capacity of HPV-transformed cancer cells. Thus, this study shows a novel function of the a-E6 oncoprotein and how it's activity might affect HPV-induced pathogenesis.

SS04 - One-dose vaccination: what do we know, what will we know and what are the remaining evidence gaps?

Crofts Jonathan
United Kingdom

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#7758

Country experiences: Going from 2 to 1 dose (United Kingdom)

39 - Public health

Background/Objectives: The Joint Committee on Vaccination and Immunisation (JCVI) is an independent expert committee that advises the UK Government on matters to do with immunisation.Starting in February 2020 JCVI went through a process of reviewing the necessary data through a series of meetings, evidence gathering and consultation which culminated in the Committees advice to move to a 1 dose schedule.The presentation will cover the key scientific evidence reviewed, issues and arguments considered and the operational challenges for the subsequent implementation of the programme in 2023/24.

Methods: JCVI first reviewed immunogenicity and efficacy data on the bivalent and quadrivalent vaccines and issued a call for evidence to support a 1 dose schedule and other alternative schedules. Emerging efficacy data from trials of 1 dose of the nine valent vaccine subsequently became available for review which was sufficient for JCVI to issue an interim statement with a stakeholder consultation advising a move to a 1 dose schedule. JCVI reviewed stakeholder feedback and further evidence from the clinical trials as well as modelling work from academic groups and the manufacturer comparing the impact of 1 dose with 2 doses before finalising its advice.

Results: After an initial decay, antibody levels plateaued and remained stable for more than 10 years. 1 dose efficacy remained high and was as good as that observed for 2 or 3 doses. A 1 dose schedule of the 9-valent vaccine was likely to have high efficacy against all included types. Modelling suggested that 1 dose vaccination had similar health benefits to 2-dose programme. The potential impact of a shorter duration of protection would be far into the future and data from clinical trials would be available to show if there was an issue with one dose before then. Stakeholder's concerns were that it was too early to move to a one dose schedule as the evidence was incomplete and that the Committee should wait until the one dose trials were completed. Any potential move should be clearly communicated to the public with sufficient lead in time for its implementation. The programme should be closely monitored, and resources should be reinvested in the adolescent vaccination programme.

Conclusions: The JCVI concluded there was enough evidence to advise a change in schedule from 2 doses to 1 dose in the routine adolescent programme. JCVI advised the programme should be closely monitored and stressed the importance of catching those girls and boys who miss their dose once the move to one dose was implemented, by ensuring there were additional opportunities in school for vaccination. The one dose schedule was implemented in September 2023.

Morhason-bello Imran
Nigeria

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#7740

One-dose vaccination: what do we know, what will we know and what are the remaining evidence gaps? Nigerian perspectives

06 - HPV prophylactic vaccines

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Background/Objectives: Cervical cancer (CC) is the second most common cancer after Breast cancer in women in Nigeria. Each year, 12,000 new cases and 8,000 deaths are associated with CC in Nigeria. Nearly 80% of women do not have access to CC screening while 80% of those with CC present with advanced disease. National HPV vaccination for eligible girls was introduced as primary prevention to reduce the huge burden of CC in Nigeria. The objective is to describe the preparation, implementation and experience/lesson learnt from the introduction of a single-dose HPV vaccination in Nigeria.

Methods: Nigeria is the most populous black nation in the world with an estimated population of 220 million people. Girls and women accounted for nearly 55% of her population. Administratively, Nigeria has 36 states, with the Federal Capital Territory (FCT) and 774 Local Government Areas (LGAs) within six geo-political regions. Since 1999, Nigeria has been running a presidential political system at the Federal, State and LGAs. The Government of Nigeria (GoN) through the Federal Ministry of Health and National Primary Healthcare Development Agency - the implementing agency - sought support from Gavi, the Vaccine Alliance and other partners to implement a single-dose vaccination for eligible girls in Nigeria using a mixed multiphase rollout plan. Following the development of a national plan, strategic response, and criteria for the selection of states, the country then developed an operational plan using hard evidence from existing data, programmes and clear indicators for the preparatory planning. The GoN introduced a single-dose Quadrivalent vaccine Gardasil after approval from the National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria, in line with WHO recommendations for low- and middle-income countries (LMICs).

Results: The HPV vaccination commenced in 15 states and FCT on October 24, 2023, targeting 7.7 million girls (80% of 9-14 years). The second phase of the HPV vaccine rollout will be in the first quarter(Q1) of 2024, and by 2025, HPV vaccination will be routine in the country. The three vaccine delivery methods that were being used include school, community, and fixed health facility vaccination methods, to cover both the in and out of schoolgirls. The 5-day vaccination campaign was followed with mop-up through walk-in and routine vaccination at designated facilities. Although 80% coverage was achieved nationally, yet three states (Lagos, Ogun, and Enugu) had coverage <80%. Some media backlashes on miscommunication and negative rumours caused some setbacks, including vaccine hesitancy. The success stories and operational challenges will be discussed.

Conclusions: Single dose HPV vaccination strategy is increasingly adopted as a primary prevention to prevent CC in LMICs including Nigeria. While Nigeria recorded a successful phase 1 rollout, there were some challenges in advocacy, communication messaging and vaccine delivery, which were addressed with multiple approaches using local solutions.

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ONE-DOSE VACCINATION: COUNTRY EXPERIENCE STAYING AT 2 DOSES (NETHERLANDS)

06 - HPV prophylactic vaccines

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Background/Objectives: All children in the Netherlands are routinely offered HPV vaccination in the year they turn 10 years old since 2022. In addition, a one-time catch-up campaign started in 2023 for teenagers and young adults up to 27 years of age. To inform the vaccination schedules to be used, the Health Council assessed whether the number of doses could be reduced from 2 to 1 dose for the age group younger than 15 years and from 3 to 2 doses for the age group 15 years or older.

Methods: The Health Council's standing committee on vaccinations conducted the review. To do so, the committee looked at data on the effectiveness of HPV vaccination as a function of number of doses from clinical trials, observational studies and programmatic vaccination in different countries. Second, the committee was able to use initial results from research specifically designed to determine the effectiveness of single-dose vaccination. The committee did not weigh the safety profile and cost-effectiveness of vaccination because these were already considered favourable regardless of a possible reduction in the number of doses.

Results: Vaccination with 2 doses may be considered non-inferior to 3 doses, but 1 dose does lead to a lower immune response than 2 or 3 doses. Specifically, single-dose vaccination results in lower antibody titres and lower levels of B-cells and memory T-cells than vaccination by 2 or 3 doses. Furthermore, 1 dose appears to protect well against infection by vaccine-targeted HPV types, but there is less certainty about the cross-protection offered by 1 dose compared with 2 or 3 doses. The evidence that protection against cervical cancer precursors may be as high after 1 dose as after 2 or 3 doses is still too limited to draw definitive conclusions.

Conclusions: Based on these data, the committee recommended a 2-dose vaccination schedule for all age groups. For the age group 15 years or older, this meant a reduction from 3 to 2 doses. For younger children, the number of doses remained the same. The committee recommended awaiting (more) results from clinical trials specifically designed to determine the effectiveness of single-dose vaccination, and also urged changes in registration to prevent off-label use.

CS01 - HPV genital diseases and treatment during pregnancy

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Management of abnormal screening

24 - Colposcopy

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Background/Objectives: The natural history of human papilloma virus infection does not change during pregnancy. There are similar rates of progression between pregnant and non-pregnant women.

Methods: Abnormal screening results should be managed using the same principles established for non-pregnant women. However, the effects of pregnancy on both cytology and colposcopy can raise difficulties in diagnosis of preinvasive cervical diseases. The reliability of Pap smear during pregnancy is related to the physiological changes of the cervical cells due to influences of hormones: degenerated decidual cells can mimic a high-grade lesion, while cells with Arias-Stella reaction can resemble those of endocervical adenocarcinoma. Colposcopy during pregnancy can also be challenging, because of cervical hyperemia, hyperplasia of endocervical glands with mucus overproduction, prolapsing vaginal walls and contact bleeding. The development of prominent normal epithelial changes can mimic the appearance of preinvasive disease. It is recommended that colposcopy during pregnancy to be performed by an experienced/expert colposcopist.

Results: Due to the fact that pregnant women represent a special group, management and therapeutic options need to have no adverse obstetrical effects. During pregnancy, the main purpose in the management of abnormal screening results is to exclude microinvasion of a cervical cancer. Both colposcopy and biopsy can be used and are considered to be safe procedures with no adverse surgical or obstetrical outcomes. When diagnosed during pregnancy, both high grade lesions (CIN 2 or 3) or adenocarcinoma in situ can be managed by surveillance by an experienced colposcopist. If excisional treatment is considered, the risk of complications is related to the type and timing of the procedure.

Conclusions: Colposcopy is recommended no sooner than four weeks after delivery. At this time, if a lesion is found, full diagnostic evaluation or excisional procedures need to be performed.

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#7653

How to manage CIN 3 discovered during pregnancy

25 - Cervical neoplasia

Background/Objectives: HPV disease in pregnancy is a complicated and a challenging problem. The investigation, colposcopy, biopsy and treatment are not well defined and controversial. The risk of cervical neoplasia to progress to invasive cancer in the pregnancy is as in non-pregnant women should be balanced again the risk of complication of treatment during pregnancy. Many of guidelines are based on studies published 40-50years ago when Knife cone was performed during all the three trimesters of the pregnancy.

Methods: Data will be presented from 26 studies that describe 1314 women over 25 years old, diagnosed with CIN 2-3 in pregnancy and during or after pregnancy invasive cervical cancer was diagnosed in 86 (6.5%) of them. Nine studies from recent years describe Laser Cone or LLETZ during the first 19 weeks of pregnancy and the complications of severe bleeding is very low and term delivery is reported in 86-100% of the women.

Results: We will present the data of a survey of the Israeli Society of Colposcopy of 173 women diagnosed with CIN 2-3 in pregnancy and during or after pregnancy invasive cervical cancer was diagnosed in 9 (6.2%) of them. 65 women underwent LLETZ during the first 15 weeks of pregnancy. Invasive cancer was diagnosed in 3(4.8%) women ,CIN 2-3 and AIS was diagnosed in 59 (90.8%) women .Severe bleeding was reported in 2(3.6%) women , abortion post LLETZ in 2 (3.6) women and term delivery was reported in 92.7 % of the 55 women who continued the pregnancy. The management of CIN 2-3 in pregnancy should be personalized according to the risk factor of the women colposcopic impression of HSIL, risk factors HPV 16,18, 45, pathological report of the cervical biopsy (positive ECC,AIS),history of persistent CIN lesion or abnormal PAP for years and women preference (fear of cancer) .

Conclusions: The complications rate is minimal during the first 15 weeks of pregnancy , and our aim is to perform LLETZ during that period. More studies are requested about the risk of CIN 2-3 to progress to cervical cancer during pregnancy and the complications of LLETZ during the first 15 weeks of pregnancy in order to write guidelines based of evidence.

References: 1.Efraim Siegler, Ofer Lavie,Amnon Amit, Zvi Vaknin, Ron Auslander, Zeev Blumenfeld, & the Israeli Colposcopy Network Should the Risk of Invasive Cancer in Pregnancy and the Safety of Loop Electrosurgical Excision Procedure During the First 15 Weeks Change Our Practice? Journal of Lower Genital Tract Disease • Volume 21, Number 4, October 2017 2.Kärrberg C, Brännström M, Strander B, et al. Colposcopically directed cervical biopsy during pregnancy; minor surgical and obstetrical complications and high rates of persistence and regression. Acta Obstet Gynecol Scand 2013;92:692-9. 3.Da Kyung Hong, Seon Ah Kim, Kyung Taek Lim, Ki Heon Lee, ... Kyeong A So Cl;inical outcome of high-grade cervical inraepithelial neoplasia during pregnancy : a 10year experience.European Journal of Obs &Gyn and reproductive Biolopgy .Volume 236, May 2019, Pages 173-176

SS08 - Microbiome

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EVIDENCE FOR VAGINAL MICROBIOME

18 - Microbiome

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Background/Objectives: The literature continues to support the role of the vaginal/cervical microbiome in the development of cervical precancers and cancers. Lactobacillus depleted microbiome has been linked to several disease states such as premature delivery, pelvic inflammatory disease and HIV acquisition. In line with these negative outcomes, Lactobacillus species (spp.) is equated with vaginal microbiome (VM) health. Lactobacillus crispatus is thought to be a primary driver in maintaining vaginal/cervical health promoting non inflammatory states whereas greater diversity with bacterial vaginosis-associated bacteria (BVAB) promoting inflammation. This latter state has been associated with progression of HPV, however, whether this inflammatory state is caused by HPV or this inflammatory state causes HPV progression remains unknown.

Methods: Data from ours and other prospective studies will be presented to begin exploring this question. One study demonstrated that HPV acquisition was not associated with inflammation but that inflammation was necessary for HPV clearance and that this inflammation was associated with a transient increase in the BVAB, Gardernella vaginalis. In that same study, having a stable Lactobacillus-dominated VM was protective against acquiring HPV. Women living with HIV have been shown to have higher rates of cervical precancers and cancers. Several studies now demonstrate that women living with HIV (WLHIV) are more likely to have Lactobacillus-depleted microbiome underscoring their vulnerability. Other studies have demonstrated that young women with CIN 2 who had microbiome dysbiosis were less likely to show CIN 2 regression. Sankey diagram showed that there was no significant difference in VM in the sample immediately prior to, and the sample immediately after regression, suggesting that CIN is not driving the VM, rather the VM may be risk factor associated with the development of CIN. This also may explain why women with treated CIN 2,3 are at risk for recurrence. This is highlighted for WLHIV who are particularly at risk for CIN 2,3 recurrence.

Results: It is plausible that Lactobacillus depleted VM may lead to a pro-inflammatory environment that can increase malignant cell proliferation and HPV E6 and E7 oncogene expression. Ongoing inflammation due to the microbial dysbiosis may then lay a toxic foundation for the development of invasive cancers.

Conclusions: Understanding the role of microbial dysbiosis and associated immune modulators and microbial toxic geno-products which can lead to cytoskeletal and DNA damage—hallmarks of the precancer high-grade squamous intraepithelial lesion (HSIL)--may lead us to the development of novel therapeutics as well as biomarkers of progression (or regression).

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#7698

ASSOCIATIONS BETWEEN THE ORAL MICROBIOME AND HEAD AND NECK CANCER RISK

18 - Microbiome

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Background/Objectives: The oral microbiome (i.e., the community of bacteria, fungi, and other microbes which live in the oral cavity) has been identified as an important component of oral health and disease. The oral microbiome has been found to be established during early childhood and is likely impacted by many environmental exposures including oral hygiene practices, diet, tobacco use, and animal exposures. A number of studies have investigated the association between the oral microbiome and head and neck cancer, but many of these studies have been cross-sectional in nature and/or had relatively small sample sizes. In this presentation, we will review the existing literature and present new opportunities for studying the association between the oral microbiome and head and neck cancer risk.

Methods: We have conducted cross-sectional studies of numerous demographic and environmental factors within prospective cohort studies, such as the Agricultural Health Study, and population-based cross-sectional studies to evaluate the associations between demographics and various exposures with the oral microbiome. We also performed a nested case-control study within the NIH-AARP Diet and Health Study to ascertain the prospective association between the oral microbiome and head and neck cancer risk using both shotgun metagenomic sequencing and ITS2 gene sequencing. We will also present data from methodological studies of the oral microbiome which can be used to plan and implement future studies.

Results: We found a number of cross-sectional associations between demographics and a variety of exposures with the oral microbiome, such as age, smoking, periodontal disease, race and ethnicity. In the nested case-control study of the oral microbiome and head and neck cancer risk, the relative abundance of bacteria related to periodontal disease was associated with a reduced risk of head and neck cancer (odds ratio [OR] 0.32; 95% confidence interval [CI]: 0.14, 0.75) and the presence of oral fungi was also associated with reduced risk of head and neck cancer (OR 0.39; 95% CI: 0.17, 0.92).

Conclusions: The oral microbiome may reflect a variety of lifetime exposures and may independently be associated with head and neck cancer risk, although the results from previous studies are generally inconsistent. There is a strong need for well-designed, prospective studies of the oral microbiome with head and neck cancer risk to understand how the oral microbiome could be used to identify individuals at increased risk of head and neck cancer or how to modify the oral microbiome to decrease the risk of head and neck cancer.

SS10 - Cervical cancer screening: harms and benefits ratio in the changing world of cervical cancer screening

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#7754

CERVICAL CANCER SCREENING: IMPACT OF RISK-STRATIFICATION IN SCREEN-INTERVALS ON THE HARMS AND BENEFITS RATIO

10 - HPV screening

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Background/Objectives: In 2023, the first birth cohort of Dutch women who were eligible for HPV vaccination was invited to participate in the cervical cancer screening program. In addition, women who participated in a previous round of primary HPV screening since 2017 have been invited again. This raises the question of whether screening can be de-intensified, by starting screening later or reducing the number of screening rounds, possibly based on HPV vaccination status or HPV test results from previous screening rounds.

Methods: We performed model-based computations to investigate whether the balance between costs, burden and health benefits of primary HPV screening could be improved by taking into account HPV vaccination status and previous HPV test results in a risk-based invitation policy. We used a microsimulation model of cervical cancer progression, which allows flexible specification of screening strategies, with HPV infection incidence based on a genotype-specific HPV transmission model. Both models were updated to reflect the latest changes in the Dutch cervical cancer screening program, recent trends in HPV prevalence and cervical cancer incidence, HPV vaccination uptake and genotype-specific efficacy. We projected costs and effects of multiple screening policies consisting of plausible combinations of risk-based screening intervals and stop and start ages.

Results: With continuation of the current screening policy, the lifetime risk of cervical cancer reduced from 633 to 294 per 100,000 women for the first 10 birth cohorts eligible for HPV vaccination. Screening efficiency decreased significantly with the influx of vaccinated cohorts, but was partially restored by reducing the number of standard screening rounds to four at ages 30, 40, 50 and 60 yrs. We found that it remains important to continue to screen at age 30 for both non-vaccinated and vaccinated women. At age 35, instead of inviting all women, invitations could be limited to women who tested HPV-positive or did not attend in the previous round, saving 1.5 million euros per 100,000 women against a neglectable increase in cancer risk. Extending such a policy to every other screening round would maximize the net monetary benefit, while the cancer risk for non-vaccinated women would still be lower than in birth cohorts ineligible for HPV vaccination. Risk-based policies based on HPV vaccination status were not cost-effective compared with risk-based invitations based on previous HPV test results.

Conclusions: Leaving the current screening program unchanged is inefficient given the reduced risk of cervical cancer in birth cohorts that are partially vaccinated. A new, uniform policy could be introduced for these cohorts in which everyone is invited for screening at ages 30, 40, 50 and 60 yrs, and the intervening rounds would count as additional screening, as would screening at age 65. Those who missed the previous round or tested HPV-positive there could be invited for additional screening. Possibly this criterion could also be used for the standard rounds. The added value of this should be weighed against the logistical challenge of having only flexible screening rounds.

CS02 - Putting anal cancer screening into practice: implementation science, biomarker development, and self-sampling

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Alan Nyitray

#8057

How might siloed biomarker development impact engagement with anal cancer screening?

10 - HPV screening

Background/Objectives: A successful anal cancer screening program will be dependent on both the identification of specific biomarkers to target persons at highest risk for disease and developing screening processes acceptable to health care providers and populations most vulnerable to anal cancer. We compared biomarker accuracy among individuals randomized to home-based self-swabbing (HBSS) or clinic-based clinician swabbing (CBCS).

Methods: In the Prevent Anal Cancer Self-Swab study, a total of 240 sexual and gender minorities who have sex with men in Milwaukee, WI, USA were randomized to anal HBSS or CBCS. Swabbing occurred at baseline and at 12 month/high-resolution anoscopy (HRA) visits for genotyping with SPF10-LiPA25, and at the HRA visit for cytology. Sensitivity, specificity, and area under the receiver operator characteristics curve (AUC) estimates were calculated for hrHPV, cytology, co-testing (hrHPV+ or abnormal cytology), and reflex testing (hrHPV+ with triage to cytology) with an outcome of high-grade squamous intraepithelial lesions or greater (≥HSIL).

Results: Median age was 46 years and 27.1% were living with HIV. Of 120 individuals randomized to HBSS, 70 returned an adequate swab at 12-months, 57.1% were positive for hrHPV, and 63 participants attended HRA with 30.2% having ≥HSIL. Of 120 randomized to CBCS, 73 provided an adequate 12-month/HRA swab, 53.4% were positive for hrHPV, and 70 participants attended HRA with 22.9% having lesions ≥HSIL. HrHPV testing and co-testing had higher sensitivity (.89, 95% CI .78-.99; .97, 95% CI .91-1.0, respectively) than reflex testing (.52, 95% CI .32-.73). AUC for hrHPV, co-testing, and reflex testing were comparable (.71, 95% CI .64-.78; .67, 95% CI .61-.72, and .71, 95% CI .59-.82, respectively). Within the HBSS and CBCS arms, accuracy for hrHPV and co-testing were comparable. Reflex testing had <.60 sensitivity in both arms. However, among people with HIV, regardless of study arm, the sensitivity of reflex testing increased to .78 (95% CI .51-1.0) and AUC increased to .89 (95% CI .74-1.0). Among HIV-negative individuals, reflex testing sensitivity was only 0.36 (95% CI .11-.61)

Conclusions: In this exploratory analysis, hrHPV testing and co-testing had high sensitivity in both HBSS and CBCS arms. Reflex testing with follow-up cytology had high sensitivity and AUC for people with HIV but not for those who were HIV-negative.

SS06 - HPV epidemiology: state of the science to inform cancer prevention

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#7841

Single-dose HPV vaccination - from discovery to policy

06 - HPV prophylactic vaccines

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Background/Objectives: More than a decade ago, investigators of the Costa Rica HPV Vaccine Trial published proof of concept that a single dose of the HPV vaccine may provide sufficient and durable protection against HPV infections. Recognizing a single dose HPV vaccine schedule would ease vaccination logistics and costs, single dose HPV vaccine schedules has been investigated in multiple clinical trials and observational studies globally. Findings have been remarkably consistent: high vaccine efficacy and immunogenicity continues to be demonstrated across populations in diverse geographies. In 2022, the WHO SAGE recommended that either one- or two-doses of HPV vaccines is sufficient for protection among males or females aged 9-20 years of age. Studies are ongoing and data continue to accrue to inform this important topic. This presentation will summarize the state of the science of single-dose HPV vaccination, present gaps in the knowledge currently exist and review ongoing studies to address outstanding questions.

Methods: --

Results: --

Conclusions: --

References: --

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#7733

CERVICAL PRECANCER - UNMASKING IN HPV VACCINATED POPULATIONS

06 - HPV prophylactic vaccines

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Background/Objectives: The first human papillomavirus (HPV) vaccine was licensed in 2006, therefore studies are now examining the long-term effects of HPV vaccination. Specifically in women, those who are HPV-vaccinated experience reductions in cervical disease and related clinical procedures, which results in more women in the population who have intact cervical transformation zones. This potentially increases the risk of cervical lesions caused by non-vaccine-preventable HPV types and together, this observational phenomenon is termed "clinical unmasking."

Methods: Because non-vaccine-preventable HPV types are less aggressive and require long-term follow-up post-vaccination to be able to observe high-grade disease endpoints, prior studies were unable to directly investigate clinical unmasking in an observational setting. We report recent results from the Costa Rica HPV Vaccine Trial that examined clinical unmasking of cervical lesions caused by non-vaccine-preventable HPV types.

Results: In the long-term follow-up of the Costa Rica HPV Vaccine Trial (years 7-11), rates of cervical lesions attributed to non-preventable HPV types were significantly higher in vaccinated versus unvaccinated women, resulting in negative vaccine efficacy for these types. Importantly, vaccinated participants still had long-term reductions in lesions overall through 11 years post-vaccination.

Conclusions: Although clinical unmasking may attenuate the long-term vaccine efficacy against cervical precancers, the observed increases were in cervical precancers caused by non-preventable HPV types, which have a lower potential for progression to cancer given their lower carcinogenicity than vaccine-preventable types. Further quantifying the magnitude of unmasking in other populations will be important to truly understand the expected impact of HPV vaccination, especially on cancer prevention.

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#7762

ANAL CANCER, FROM EPIDEMIOLOGY TO PREVENTION

27 - Anal neoplasia

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Background/Objectives: Anal cancer is an HPV-driven malignancy with over fifty thousand cases globally in 2020 and has increased in incidence for the last several decades. Fortunately, the ANCHOR trial has shown that the treatment of anal precancer detected through screening with high-resolution anoscopy can effectively reduce the risk of anal cancer. However, few national guidelines have been established regarding implementation strategies for screening. This talk with summarize the evidence from observational studies on the incidence of anal precancer and invasive cancer for males and females with and without HIV.

Methods: We will present risk estimates among people with HIV according to HIV-acquisition risk factor, prior diagnosis of AIDS, time since HIV or AIDS diagnosis, and age. We will then describe trends in the incidence of anal precancer among people with and without HIV according to sex, and within group characteristics that are associated with incidence of anal precancer. We will describe screening strategies and algorithms used to identifying individuals who would benefit the most from HRA. We will describe possible screening strategies related to age, frequency, and referral algorithms based on HPV testing and biopsy results.

Results: Among people with HIV, incidence of anal cancer is highest among MSM compared to other males or females with HIV.1 Additionally, those with a prior diagnosis of AIDS had the highest incidence compared to those with HIV alone, and time since AIDS diagnosis was a stronger determinant of anal cancer risk than age. Men and women with and without HIV have seen increasing trends in the incidence of anal precancer.2 Among those with anal precancer, the subsequent risk of invasive anal cancer appeared similar across groups, with possibly lowest incidence for those with HIV but who have not progress to a diagnosis of AIDS.

Conclusions: Increased incidence of anal precancer indicate positive gains in anal cancer screening across groups. People with HIV, particularly MSM who have had a diagnosis of AIDS more than 10 years ago, should be prioritized for receiving HRA. Additionally, MSM without HIV and women with gynecologic precancers may benefit from anal cancer screening. However, more work is required to determine age at screening and the potential role of other screening modalities to triage for referral to HRA.

References: PLEASE NOTE: This abstract is submitted in reference to an invited speaker presentation - Title: Newest insights into HPV epidemiology. 1. Haas CB, Engels EA, Horner MJ, Pfeiffer R, Luo Q, Kreimer A, Palefsky JM, Shiels M. Cumulative incidence of anal cancer since HIV or AIDS diagnosis in the United States. J Natl Cancer Inst. 2023. Epub 20230703. doi: 10.1093/jnci/djad128. PubMed PMID: 37399095. 2. Haas CB, Engels EA, Palefsky JM, Clarke MA, Kreimer AR, Luo Q, Pfeiffer RM, Qiao B, Pawlish KS, Monterosso A, Shiels MS. Severe anal intraepithelial neoplasia trends and subsequent invasive anal cancer in the United States. J Natl Cancer Inst. 2023. Epub 20230826. doi: 10.1093/jnci/djad176. PubMed PMID: 37632787.

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#7850

Oropharyngeal Cancer by World Region - Changing Etiologic Fractions

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Globally, oropharyngeal cancer (OPC) exhibits disparities influenced by diverse risk factor profiles, reflecting the impact of changing etiologic fractions in recent decades.Traditionally associated with tobacco and alcohol, OPC has experienced a notable transformation due to the increasing prevalence of human papillomavirus (HPV). This shift is evident in rising global incidence rates in several countries and dynamic trends worldwide reflecting the influence of HPV. Age-standardized incidence rates for OPC vary widely across countries, with the highest rates observed in France for men (19.7 cases/100,000 people) and Germany for women (5.2 cases/100,000 people), while the lowest rates observed in Kuwait for men (0.7 cases/100,000 people) and Bahrain for women (0.1 cases/100,000 people) from 1993 to 2012. During the same period, a statistically significant rise was observed in OPC incidence across several countries, with annual percent increases exceeding 3% per year in men from 19 countries and women from 13 countries. Rigorous methodologies in data collection and analysis are essential for accurate epidemiologic assessments, ensuring a valid interpretation of the true impact of evolving etiologic fractions on OPC incidence. Variations in OPC incidence observed globally, underscore the need for targeted prevention and intervention. The current landscape emphasizes HPV as a predominant risk factor, demanding comprehensive surveillance to adapt to OPC's dynamic nature. Understanding the burden, trends, and evolving etiologic fractions of OPC is crucial for effective public health strategies. Ongoing research and surveillance are essential to adapt prevention and intervention measures such as HPV vaccination, to address the changing landscape of this cancer.

Methods: xx

Results: xx

Conclusions: xx

References: Selected reading articles = 1. Zumsteg, Z. S., Luu, M., Rosenberg, P. S., Elrod, J. K., Bray, F., Vaccarella, S., Gay, C., Lu, D., Chen, M., Chaturvedi, A. K., & Goodman, M. (2023). Global epidemic patterns of oropharyngeal cancer. Journal of the National Cancer Institute, 115(12), 1544-1554. https://doi.org/10.1093/jnci/djad169 2. Castellsague X, Alemany L, Quer M, Halec G, Quiros B, Tous S, et al. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. J Natl Cancer Inst. 2016;108(6):djv403. doi: 10.1093/jnci/djv403 3. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide Trends in Incidence Rates for Oral Cavity and Oropharyngeal Cancers. Journal of Clinical Oncology. 2013;31(36):4550-9. doi: 10.1200/jco.2013.50.3870

SS11 - HPV type replacement

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#7734

CLINICAL UNMASKING OF CERVICAL PRECANCERS CAUSED BY NON-VACCINE-PREVENTABLE HPV TYPES FOLLOWING HPV VACCINATION: A PROOF-OF-CONCEPT IN THE COSTA RICA HPV VACCINE TRIAL

06 - HPV prophylactic vaccines

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Background/Objectives: Evaluations on clinical unmasking of cervical precancers caused by non-vaccine-preventable human papillomavirus (HPV) types following HPV vaccination requires long-term follow-up post-vaccination because non-vaccine-preventable HPV types have much slower progression rates. The Costa Rica HPV Vaccine Trial is well positioned to examine whether clinical unmasking is a real phenomenon due to the long-term follow-up of 11 years post-vaccination.

Methods: In the Costa Rica HPV Vaccine Trial, we calculated efficacy of the AS04-adjuvanted HPV vaccine against cervical lesions caused by non-vaccine preventable HPV types, vaccine-preventable types, and all lesions irrespective of type, through 11 years post-vaccination.

Results: The rate of cervical lesions attributed to non-preventable types was significantly higher in the HPV-vaccine arm compared to the unvaccinated control group. However, there were still significant relative and absolute reductions in cervical precancers overall irrespective of HPV type among vaccinated women compared with unvaccinated women.

Conclusions: We provide a proof-of-concept that clinical unmasking may be a real phenomenon, however the HPV vaccine's protection still far outweighs the additional risk of cervical lesions caused by non-preventable HPV types. Increased vaccine valency and the shift toward

HN01 - HPV and Head & Neck Forum - Submitted papers I

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#6541

FEASIBILITY STUDY ONCSALIVA - NON-INVASIVE SPECIMEN FOR THE DETECTION OF HEAD AND NECK CANCER VIA EPIGENETIC BIOMARKERS

15 - Molecular markers

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Background/Objectives: Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease, encompassing malignancies arising from hypopharynx, oropharynx, the nasal and oral cavities, or the larynx. Two thirds of patients are diagnosed with advanced tumour stages. The gold standard for diagnosis of HNSCC is still a biopsy of the suspicious lesion. Since invasive procedures are adverse as screening routines and for clarification of symptoms, sensitive diagnostic tools for early detection need to be established. Therefore, we want to leverage easy accessibility of non-invasive samples, such as saliva and oral swabs. We established an qPCR-based DNA methylation-specific assay detecting five tumour markers. Within the framework of the feasibility study OncSaliva, we assessed the use of non-invasive specimen for molecular diagnostic testing for tumour-specific epigenetic markers, which could be useful for early diagnosis and postoperative recurrence risk assessment in clinical routine.

Methods: Study specimens are collected at three different German clinics for Otorhinolaryngology, mainly at the Jena University Hospital. Non-invasive specimens are collected pre-surgery and during post-surgical routine examinations. Further, fresh-frozen tissue samples are collected from HNSCC patients and controls. DNA isolated from all samples is bisulfite-converted before use in methylation-specific multiplex qPCR, for analysis of differentially methylated regions specific for HNSCC. Five markers ZNF671, ZNF833, ZIC1, PAX6-1, HOXA9 and bisulfite-specific reference Beta-Actin are analyzed in all specimens. The goal is to include 100 control individuals and 100 HNSCC patients, the latter with two-year follow-up examination.

Results: By now we have analyzed fresh-frozen tissue and saliva from 51 HNSCC patients and 33 controls in the OncSaliva study. Swab samples are available for 14 HNSCC patients and 15 controls. For tissue samples DNA methylation markers showed 75% sensitivity and 100% specificity, if three of five markers were required to test positive. Single-marker detection offered up to 83% sensitivity with 97% specificity in tissue. In saliva the best single marker resulted in 71% sensitivity and 82% specificity. If three out of five markers were to be positive in saliva, 63% sensitivity and 91% specificity could be reached. Comparison of tissue and saliva sample pairs yielded 49% to 78% agreement for the HNSCC group and 73% to 100% agreement in the control group. Swab samples showed a 57% sensitivity and 93% specificity, if three of five markers were required to test positive. Comparison of tissue and swab sample pairs yielded 57% agreement for the HNSCC group and 93% agreement in the control group. Data from individual patient follow-ups will be presented at the congress.

Conclusions: Preliminary results of the ongoing study support our hypothesis that DNA methylation analysis can robustly detect HNSCC in both, tissues and non-invasive specimens. Utilization of easily acquired cancer cells for detection of HNSCC from saliva and oral swab samples can serve as a useful, cost effective and easy method for cancer-specific diagnostic assays. These will be primary for the development of in vitro diagnostics aiming at secondary and tertiary prevention.

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#6614

DIAGNOSTIC ACCURACY OF HPV16 EARLY ANTIGEN SEROLOGY FOR HPV-DRIVEN OROPHARYNGEAL CANCER IS INDEPENDENT OF AGE AND SEX

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: A growing proportion of head and neck cancers (HNC), especially oropharyngeal cancer (OPC), is caused by human papillomavirus (HPV). There are several biomarkers separating HPV-driven HNC from non-HPV-driven HNC, such as HPV DNA detection by PCR or by in situ hybridisation (ISH), and p16INK4a immunohistochemistry (p16). Each of these markers has their own benefits and limitations. A relatively new biomarker, mostly used for HPV-driven OPC, is HPV early antigen serology, especially for E6 oncoprotein antibodies. We aimed to investigate the diagnostic accuracy of HPV serology and its performance across patient characteristics.

Methods: Data from the VOYAGER consortium was used, which comprises five studies on HNC from North America and Europe. Diagnostic accuracy, i.e., sensitivity, specificity, Cohen's kappa and correctly classified proportions of HPV16 E6 serology, was assessed for OPC and other HNC using p16, ISH and PCR as reference methods. Stratified analyses were performed for variables including year of diagnosis, age, sex, BMI, smoking and alcohol use, to test the robustness of diagnostic accuracy. Finally, a risk-factor analysis was conducted, to assess risk-factors for HPV-driven compared to non-HPV-driven OPC.

Results: In total, the study population consisted of 6,809 HNC patients with serology details. Of these, 3,266 (48%) had OPC. Overall, HPV serology had a sensitivity of 86.8% (95%CI 85.1-88.3) and specificity of 91.2% (95%CI 88.6-93.4) for HPV-driven OPC using p16 as reference method. For PCR, a comparable diagnostic accuracy was found (sensitivity: 83.8%; specificity: 93.8%), although the specificity with ISH as reference was lower (sensitivity: 90.6%; specificity: 58.0%). In stratified analyses, diagnostic accuracy remained consistent across strata of most variables such as sex and different age groups. Sensitivity was lower for heavy smokers (77.7%), OPC without lymph node involvement (74.4%) and the ARCAGE study (66.7%), while specificity decreased for cases with inf10 packyears (72.1%). The risk-factor model included study, year of diagnosis, age, sex, BMI, alcohol use, packyears, TNM-T and TNM-N stage.

Conclusions: HPV serology is a robust biomarker for HPV-driven OPC, and its diagnostic accuracy is independent of age and sex. Future research is suggested on the influence of smoking on HPV antibody levels.

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#6848

Quantification of Human Papillomavirus cell-free DNA from low volume blood plasma samples by digital PCR

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The incidence rate of human papillomavirus-driven oropharyngeal cancer (HPV-OPC) is increasing in many countries with high human development index. HPV cell-free DNA (cfDNA) isolated from relatively large amounts of blood plasma (typically 3-4 ml) has been successfully used for therapy surveillance of HPV-OPC patients. A currently highly discussed application of HPV-cfDNA is early detection of HPV-OPC in symptom-free individuals. This requires particularly sensitive and specific cfDNA detection methods as viral copy numbers can be very low. To study the predictive power of pre-diagnostic HPV-cfDNA, archived samples from epidemiological cohorts with limited plasma volume are an important source.

Methods: To establish a cfDNA detection workflow optimized for low plasma volumes we compared two cfDNA purification methods (MagNA Pure 96 cfNA ss 2000 protocol and QIAamp ccfDNA/RNA) and two digital PCR systems (Biorad QX200 and QIAGEN QIAcuity One). The digital PCR assay utilizes primers and probes targeting HPV16 E6, HPV16 E7, HPV33 E6 and the human control gene beta-globin. Final assay validation included 65 low volume plasma samples from OPC patients with defined HPV status (34 HPV16+, 1 HPV33+, 2 HPV58+, 28 HPV-negative) stored for 2-9 years.

Results: MagNA Pure 96 cfNA ss 2000 protocol yielded a 28% higher cfDNA isolation efficiency in comparison to the QIAamp ccfDNA/RNA kit. Both digital PCR systems showed comparable analytical sensitivity (detection limits 6-17 copies for both HPV16 and HPV33), but the higher multiplexing capacity allowed the QIAcuity to detect both HPV types in the same assay. In the validation set, the assay had a sensitivity of 80% (n=28/35) for detecting HPV16 and HPV33, and a specificity of 97% (n=29/30). In samples with ≥750 µl plasma available, the sensitivity was 85% (n=17/20), while in samples with ≤750 µl plasma the sensitivity was 73% (n=11/15).

Conclusions: Despite the expected drop in sensitivity with decreased plasma volume, the assay is sensitive and highly specific even in low volume samples, and thus suited for studies exploring HPV-cfDNA as an early HPV-OPC detection marker in low volume archival material.

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#6892

Liquid biopsies with circulating plasma HPV-DNA measurements - a clinically applicable surveillance tool for HPV-positive oropharyngeal cancer patients

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The objective was to evaluate the accuracy of cell-free human papillomavirus-DNA (cfHPV-DNA) measurements in liquid biopsies in predicting disease in HPV+/p16+ oropharyngeal squamous cell carcinoma (OPSCC) patients.

Methods: This is a prospective cohort study. Plasma samples were collected before treatment, and serially after curative intended therapy at follow-up visits 2 weeks, and 6, 9, 12, 18, 24, and 30 months after treatment. A Droplet Digital (dd)PCR assay comprising eight HPV genotypes was used. HPV genotypes found in plasma and tumour tissue were compared. We correlated biopsy- or imaging-verified tumour progression to cfHPV-DNA in follow-up samples.

Results: We enrolled 72 HPV+/p16+ OPSCC patients. Baseline sensitivity for cfHPV-DNA detection was 97.2% (95% CI 90.3%-99.6). CfHPV-DNA copy number/millilitre plasma correlated with tumour stage. We found a 100% concordance between HPV genotype in tumour tissue and plasma. Fifty-four patients were followed with serial blood samples for a median of 19.7 months (Interquartile Range: 13.5-25.5 months). Forty-one patients had undetectable plasma cfHPV-DNA in all follow-up samples, and none developed recurrences. Thirteen patients were classified as cfHPV-DNA positive in a follow-up plasma sample. Of these, five patients developed a recurrence, and three had residual cancer. It was possible to detect cfHPV-DNA in plasma 97-166 days prior to the proven recurrence.

Conclusions: Our study, comprising the largest study of HPV+/p16+ OPSCC patients, using an ultrasensitive multiplex HPV gene panel, revealed a high sensitivity of cfHPV-DNA detection in the liquid biopsies. We recommend serial plasma HPV samples for clinical monitoring of HPV+/p16+ OPSCC patients.

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#7136

SEX DISPARITIES IN HUMAN PAPILLOMA VIRUS-ASSOCIATED OROPHARYNGEAL CARCINOMA DE-ESCALATION THERAPY CLINICAL TRIALS

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Sex disparities in human papillomavirus (HPV) associated oropharyngeal carcinoma have emerged as a critical concern in recent years. This study investigates de-escalation therapy clinical trials, aiming to uncover potential variations between male and female sex. By examining these disparities, we can refine therapeutic strategies to ensure more equitable and effective care for all patients. Our objective is to identify the representation of sex in clinical trials for de-escalation therapy for human papillomavirus-associated oropharyngeal carcinoma.

Methods: The literature was searched for published clinical trials about de-escalation therapy for HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). De-escalation clinical trials that included participants' demographics were identified. Analysis of proportions for sex was done. Proportions for sex were compared with the general US HPV-associated OPSCC population.

Results: Data for 14 de-escalation clinical trials (N=2587) was extracted. Of the trials used, 92% reported sex/gender. Of those trials that reported sex/gender, Figure 1 shows that the proportion of women included was 11.8% ([95%CI: 9.4% to 14.7%]). Within the de-escalation trials that reported sex/gender, none stratified their results by sex. While women accounted for 30% of HPV-associated OPSCC patients in the US, they represented 12% of participants in studies that reported sex.

Conclusions: The current cancer treatment guidelines are developed based on clinical trials that may not accurately represent the patients we apply them to. Even though previous literature has shown women may have better outcomes in HPV-associated OPSCC, no de-escalation trial has tried to characterize results by sex/gender. Patients of the female sex may have biologically distinct tumors and tumor microbiomes but are treated as a one-size-fits-all. Subsequently, this lack of characterization of treatments can lead to more aggressive treatment than is necessary for this population, which potentially causes worse adverse events. This shows a need for clinical trials to report sex-specific outcomes that could lead to a better understanding of this population.

Figure 1

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#6521

TREATMENT AND PROGNOSTIC DIFFERENCES IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA IN TWO HIGH-PREVALENCE HPV AREAS WITH DISTINCT HEALTHCARE SYSTEMS: A CROSS-COUNTRY COMPARISON BETWEEN THE USA AND DENMARK

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human papillomavirus (HPV) is a key factor in the rising incidence of oropharyngeal squamous cell carcinoma (OPSCC) worldwide, but with great geographical variation (1-7). Both the U.S. and Denmark are HPV high-prevalence areas (8,9) but with distinct healthcare systems. Uncertainty exists regarding potential treatment and clinical differences that are crucial to consider when comparing the survival in oropharyngeal squamous cell carcinoma (OPSCC) cohorts across different geographical areas and with different healthcare systems and practice patterns. The aim of this study was to identify clinical, treatment and prognostic differences among OPSCC patients in two HPV high-prevalence areas with health care systems.

Methods: Patients diagnosed with OPSCC from 2015-2020 were included from The University of Texas MD Anderson Cancer Center (UTMDACC), USA and from The University Hospital of Copenhagen, Denmark from 2015-2020, (n=2484). Outcomes were 5-year overall survival (OS) and recurrence-free survival (RFS). Subgroup analyses were made stratified by treatment regimen (radiotherapy (RT) alone/chemoradiotherapy (CRT)/surgery alone/surgery + RT/CRT). and for low risk OPSCC patients (T1-2N0M0) and high-risk patients (UICC8 III-IV).

Results: Preliminary results show that there were significantly more HPV+ (88.2% vs. 71.5%), males (8.4:1 vs. 2.9:1), never-smokers (52.1% vs. 23.7%), lower UICC8-stage (I/II: 78.4% vs. 69.2%) in the UTMDACC cohort. Significantly more received single modality RT or surgery alone in the Copenhagen cohort (30.3% vs 14.8% and 16% vs 8.7%). Equivalent CRT usage was observed in the two cohorts (49.8% vs 51%), but additionally 16.7% received neoadjuvant +RT/CRT in the UTMDACC cohort. No prognostic difference in the adjusted OS was observed (hazard ratio [HR] of 1.30, p=0.09), but a significantly increased RFS HR was observed for the Copenhagen cohort (HR 1.65, p=0.006). No difference in prognosis was observed for low-risk patients, but the prognosis for high-risk patients in the Copenhagen cohort was worse (OS HR 2.27, p=0.003, RFS HR 2.43, p=0.01). Survival data of subgroup analyses by treatment regimen is to be presented.

Conclusions: The study revealed significant differences in clinical characteristics and treatment modalities given, reflecting a substantial difference in patient populations and practice patterns. This is important to acknowledge when comparing the prognosis in different OPSCC cohorts. In addition, our results emphasize the significance of meticulous patient selection when considering both de-escalated and escalated strategies in various geographic areas and practice settings, as achieving reproducibility could prove challenging.

References: 1. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24-35. doi:10.1056/NEJMoa0912217 2. Gillison ML, Koch WM CR. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709-720. 3. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009;10:321-322. doi:10.1016/S1470-2045(09)70096-8 4. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J cancer. 2019;144(8):1941-1953. doi:10.1002/ijc.31937 5. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide Trends in Incidence Rates for Oral Cavity and Oropharyngeal Cancers. J Clin Oncol. 2013;31(36):4550-4559. doi:10.1200/JCO.2013.50.3870 6. Carlander AF, Jakobsen KK, Bendtsen SK, et al. A Contemporary Systematic Review on Repartition of HPV-Positivity in Oropharyngeal Cancer Worldwide. Viruses. 2021;13(7). doi:10.3390/v13071326 7. Mehanna H, Taberna M, von Buchwald C, et al. Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis. Lancet Oncol. Published online 2023:239-251. doi:10.1016/S1470-2045(23)00013-X 8. Garset-Zamani M, Carlander AF, Jakobsen KK, et al. Impact of specific high-risk human papillomavirus genotypes on s

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#6720

PRELIMINARY FINDINGS FROM A MULTI-CENTRE STUDY ON HUMAN PAPILLOMAVIRUS DRIVEN HEAD AND NECK SQUAMOUS CELL CARCINOMAS IN A MULTI-ETHNIC SOCIETY

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Head and neck squamous cell carcinoma (HNSCC) is the most common type of head and neck cancer. A subset of HNSCC is driven by human papillomavirus (HPV). HPV driven HNSCC especially involving the oropharynx, has been on the rise in recent years, particularly in the West. Currently, there is a lack of data on the burden of HPV driven HNSCC in Asian countries particularly multi-ethnic societies such as Malaysia.

Methods: A cross-sectional multicentre study with tissue analysis of Malaysian patients diagnosed with primary HNSCC between 01/01/2016 to 31/12/2020 was undertaken. Determination of HPV status was carried out using p16INK4a immunohistochemistry (IHC), detection of HPV-DNA in conjunction with HPV genotyping and detection of high-risk HPV (HR-HPV) mRNA in-situ hybridization (RNA-ISH) on archived formalin-fixed paraffin-embedded (FFPE) tissue. Cases with discordant results between HPV-DNA and p16INK4a IHC were resolved using HR-HPV RNA-ISH.

Results: Of the 356 cases identified, analysis has been completed for 311 cases to date. Overall, median age at diagnosis was 60.0 years (IQR = 16) and 72.0% of patients were males. In this cohort, 43.1% of patients were Chinese, 25.4% were Malay, 24.4% were Indian and 7.1% were from other ethnicities. Estimated prevalence of HPV-driven HNSCC using a tiered testing algorithm was approximately 14.5% regardless of subsite. Unsurprisingly, approximately 30.5% of cases originating from the oropharynx were HPV-driven. Age at diagnosis and sex of patients were not statistically significant in relation to HPV status of HNSCC ($p > 0.05$). Most of the HPV-driven disease was seen in patients of Chinese ethnicity (62.2%; $p = 0.005$; Fisher-Freeman-Halton Exact test). All HPV-driven HNSCC had only high-risk HPV genotypes and HPV 16 was the most frequently encountered. Several cases had more than one HPV genotype (11.1%). Discordance between HPV-DNA and p16INK4a IHC was seen in approximately 13.2% of cases.

Conclusions: Preliminary findings suggest that the proportion of HPV-driven HNSCC in Malaysia is lower than reported in Western cohorts. Patients with HPV-driven disease do not seem to be younger than patients with HPV-negative disease. Molecular testing for HPV DNA or E6/E7 mRNA in addition to p16INK4a IHC in a tiered algorithm is advisable to determine true HPV-driven head and neck cancers prior to mapping out treatment plans for these patients.

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#7163

Prevalence of cystic metastases and HPV in a consecutive cohort of surgically removed branchial cleft cysts.

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Solitary cystic lesion of the neck may often be the only initial presenting symptom for branchial cleft cysts and cystic metastases. The aim was to analyse the malignancy rate detected in patients undergoing surgical treatment for lateral branchial cleft cyst and if the negative HPV together with benign cytology can be used as a predictive marker for benign cystic neck lesions.

Methods: The records of all patients >18 years of age with surgical procedure code ENB40 (Excision of lateral branchial cleft cyst- or fistula) between 2003-2023 were reviewed. After excluding 113 patients, 440 patients were included for final analysis. Re-evaluation of the cytology including HPV-analysis was performed in those who had a malignant cyst.

Results: Cystic metastases were demonstrated histologically after surgical excision in 15 patients, with a calculated prevalence of cystic metastasis of 3.4% for patients over 18 years of age regardless of the primary tumour type. Four of the patients had primary papillary thyroid cancer and nine had metastatic squamous cell carcinoma.

Conclusions: When the investigation protocol for solitary cystic lesions of the neck is followed, the negative predictive value for malignancy is 97%. All adult patients with a cytologic verified diagnosis of branchial cyst should be examined with HPV-analysis of the cystic sample before excision of the cyst. Failure of predicting a malignancy is often associated with cytology of poor cellularity which may be improved by more frequent use of ultrasound guided fine needle aspiration cytology.

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#7024

CLINICAL BENEFIT FOLLOWING ADJUVANT THERAPEUTIC VACCINATION WITH PRGN-2012 IS GOVERNED BY THE PAPILLOMA MICROENVIRONMENT IN PATIENTS WITH RRP

07 - HPV therapeutic vaccines

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Background/Objectives: Recurrent respiratory papillomatosis (RRP) is caused by chronic infection with human papillomavirus (HPV) 6 or 11 yet is treated with repeat surgical debulking. No approved medical therapies exist. Non-surgical treatment that addresses the underlying infection to control papilloma formation and growth is needed to prevent disease recurrence and minimize the morbidity associated with repeat surgical interventions.

Methods: We have developed and clinically studied PRGN-2012, a novel gorilla-adenovirus therapeutic vaccine encoding HPV 6 and 11 antigens for the treatment of RRP. Early phase clinical study of the safety and efficacy of the vaccine as well as immune correlatives of response are complete.

Results: Fifteen adults with RRP (median age 51 years) that required three or more clinically indicated interventions in the 12 months prior to study enrollment (median number of interventions 6, range 3-10) were treated in a phase 1 study. Median number of lifetime interventions prior to study enrollment was 32 (range 9-300+). A course of adjuvant vaccination with PRGN-2012 after initial surgical debridement, consisting of four subcutaneous injections over a three-month period, was safe and well tolerated. Grade 1 injection site reaction, fatigue and malaise were the most frequent adverse events. All patients completed the study treatment. Complete response, defined as no need for clinically-indicated intervention in the 12 months after the clinical trial, was observed in 6 of 12 (50%) patients treated at the phase 2 dose (5x1011 viral particles per injection). Neutralizing antibody titers against the vaccine remained low despite multiple administrations. Although HPV-specific T cell responses in the peripheral blood to at least one HPV antigen increased after vaccination in all patients, the observed increase was greater in responders compared to non-responders. Induction of peripheral polyclonal HPV-specific T cell responses after vaccination were common. Papillomas in responders were infiltrated by HPV-specific T cells that were not detected prior to treatment. Further single-cell transcriptomic and proteomic study of papilloma biopsies revealed a high CXCL9/CXCL8 ratio associated with greater T cell infiltration and reduced mean HPV gene expression per papilloma cell in responders. Conversely, studies revealed a low CXCL9/CXCL8 ratio associated with low T cell infiltration, high neutrophil infiltration and greater mean HPV gene expression per papilloma cell in non-responders.

Conclusions: Adjuvant therapeutic vaccination with PRGN-2012 is safe and results in clear clinical benefit in 50% of treated RRP patients. Although all patients appear to develop increased peripheral blood HPV-specific T cell responses after vaccination, the state of the papilloma microenvironment appears to govern papilloma T cell trafficking and activity. A pivotal, registration phase 2 clinical study aimed at validating the clinical efficacy of adjuvant PRGN-2012 in adults with RRP is ongoing.

SS12 - Gender neutral vaccination: impact on speed of elimination and subsequent need for screening

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#7735

Changing HPV prevalence changes the optimal screening program to use

39 - Public health

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Background/Objectives: Gender-neutral vaccination against HPV infection has been introduced across high-income countries and in some middle-income countries to ensure that population-level impact of vaccination is maximised and would eventually lead or contribute to cervical cancer elimination in targeted birth cohorts. Vaccinated birth-cohort are progressively reaching the age-range of cervical cancer screening. To optimise resource allocation and minimize adverse effect of screening, protocols will need to be progressively adapted to account for the individual and collective reduced risk of cervical cancer in vaccinated birth-cohorts. Accurate data from vaccination and screening programmes will be essential to inform public health decision models and to support the design of risk-stratified screening protocols. Such protocols to be realistic will have to account for context-specific opportunities and constraints. The objective of this presentation is to illustrate, using information from Sweden and the Kingdom of Bhutan, a middle-income country in which both HPV vaccination and HPV-DNA based cervical cancer screening are extensively implemented, the opportunities and challenges of screening of HPV-vaccinated birth cohorts.

Methods: To project the expected impact of risk-stratified screening among vaccinated-birth cohorts, we inform HPV transmission and progression models with data describing demographic, behavioral, and epidemiological characteristics of the populations as well as with figures descriptive of the performances of vaccination and screening program. Projections are obtained using the METHIS (ModElling Tools for HPV Infection-related cancers) modelling platform developed at IARC.

Results: Sweden has introduced quadrivalent HPV vaccination in year 2010 targeting 11-year-old girls, the coverage ranged between 73% and 83%, in year 2016 and 2022, respectively. Gender-neutral vaccination was introduced in year 2021 and coverage of boys has reached 77%. Sweden has launched HPV-DNA based screening in 2015, the target age-range is 23-70 years, the screening coverage is 82-83% (2021), and regions may choose if they want to use self-collection or sampling by healthcare personnel as the first sampling method. Bhutan has introduced quadrivalent HPV vaccination in year 2009 targeting 12-year-old girls, the coverage ranged between 74% and 90%, in year 2011 and 2021, respectively. Gender-neutral vaccination was introduced in year 2021 and coverage of boys has reached 82%. Bhutan has launched HPV-DNA based screening in the year 2021, the target age range is women aged 30-65 years old, the screening coverage is 90.8%, and sampling by healthcare personnel is the first sampling method. Demographic, behavioral, and epidemiological useful to inform METHIS have been previously presented elsewhere and will be summarized during the presentation.

Conclusions: Coverage of HPV vaccination as well as cervical cancer screening are very high in both Sweden and Bhutan. Both countries are heading towards cervical cancer elimination and entering a transition phase, in which cervical cancer screening will have to account for the background risk of cervical cancer of women. To optimise resource allocation and minimize adverse effect of screening, data from each country will be soon used to inform a public health decision modelling platform to design context-responsive realistic, and affordable, risk-stratified screening programs.

SS15 - Screening for HPV-related cancer in sexual and gender minority adults

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#7763

ANAL CANCER RISK AND SCREENING STRATEGIES IN MSM WITH AND WITHOUT HIV

27 - Anal neoplasia

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Background/Objectives: Anal cancer is an HPV-driven malignancy with over fifty thousand cases globally in 2020. The greatest burden of anal cancer is among individuals with HIV and specifically gay, bisexual and other men who have sex with men (MSM). Fortunately, promising new evidence from the ANCHOR trial, conducted among people with HIV, has shown that the treatment of anal precancer detected through screening with high-resolution anoscopy (HRA) can effectively reduce the risk of anal cancer. This talk will summarize the evidence from observational studies on the incidence of anal precancer and invasive cancer among MSM.

Methods: We will present risk estimates among people with HIV according to prior diagnosis of AIDS, time since HIV or AIDS diagnosis, and age. We will then describe trends in the incidence of anal precancer among people with and without HIV. As there is limited clinical capacity for performing HRA, we will briefly discuss the potential implementation of HPV testing, the performance and role of cytology, self-testing applications, and clinician uptake of digital anorectal. We will briefly describe existing guidance on anal cancer screening and the evidence needed to inform future national guidelines.

Results: Among people with HIV, incidence of anal cancer is highest among MSM compared to other males or females with HIV.1 Additionally, those with a prior diagnosis of AIDS have the highest cumulative incidence compared to those with HIV alone and time since AIDS diagnosis was a stronger determinant of anal cancer risk than age. We have seen significant increases in the rates of anal cancer diagnosed among men with and without HIV, as well as other groups.2 However, we also have observed similar risk for invasive anal cancer following precancer for men with a diagnosis of AIDS as for men without HIV, and suggested evidence of a lower cumulative incidence for men with HIV alone.

Conclusions: In settings where demand for HRA exceeds clinical capacity, the existing evidence suggests that MSM with a prior diagnosis of AIDS should be prioritized with consideration of time since AIDS diagnosis. Systematic collection of sexual orientation and gender identity in registry and clinical databases will be essential to better estimating the risk of anal cancer in MSM without HIV.

References: PLEASE NOTE: This abstract is submitted in reference to an invited speaker presentation - Title: Screening for HPV-related cancer in sexual and gender minority adults. 1. Haas CB, Engels EA, Horner MJ, Pfeiffer R, Luo Q, Kreimer A, Palefsky JM, Shiels M. Cumulative incidence of anal cancer since HIV or AIDS diagnosis in the United States. J Natl Cancer Inst. 2023. Epub 20230703. doi: 10.1093/jnci/djad128. PubMed PMID: 37399095. 2. Haas CB, Engels EA, Palefsky JM, Clarke MA, Kreimer AR, Luo Q, Pfeiffer RM, Qiao B, Pawlish KS, Monterosso A, Shiels MS. Severe anal intraepithelial neoplasia trends and subsequent invasive anal cancer in the United States. J Natl Cancer Inst. 2023. Epub 20230826. doi: 10.1093/jnci/djad176. PubMed PMID: 37632787.

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#7760

Cervical cancer screening among transgender men and non-binary people in the United Kingdom

10 - HPV screening

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Background/Objectives: Transgender men and non-binary (TMNB) people with a cervix are at risk for cervical cancer but may be less likely than cisgender women to have ever undergone screening for cervical cancer due to barriers at the personal and system levels. TMNB patients may avoid pelvic exams due to increased pain, worsening of gender dysphoria (distress associated with the disconnect between identity and sex assigned at birth), or medical mistrust. Clinicians may not recommend screening for TMNB patients due to incorrect assumptions about their anatomy or sexual behavior. Medical systems may also fail to send invites to TMNB patients when they change their gender from female to male in the medical record. We sought to examine the prevalence cervical cancer screening among TMNB patients registered with a general practitioner.

Methods: We used data from the Clinical Practice Research Datalink (CPRD), a primary care database in the United Kingdom, to estimate the likelihood of having ever received cervical cancer screening among TMNB compared to cisgender women. TMNB patients were matched to 20 cisgender women from the same practice on age. We searched the medical records of patients aged 25-65 years old (eligible screening age) between 2003-2020, for evidence of cervical cancer screening. We excluded those with hysterectomy coded in their medical records. We used conditional logistic regression to estimate odds ratios and 95% confidence intervals (CI) adjusting for age and race.

Results: Among the 9,726 CPRD patients there were 528 TMNB matched to 9,198 cisgender women. The average age of TMNB patients was 34.3 years and of cisgender women was 34.9 years (P=0.186). TMNB patients were more likely than cisgender women to be White (78.0% vs 88.7%, P<0.0001) and to be from England (94.5% vs. 88.7%; P<0.0001). TMNB were less likely to have evidence of cervical screening than cisgender women (32.2% vs. 79.8%; P<0.0001). Accounting for the matched design, age, and race, cisgender women were 8.1 (95% CI: 6.4 - 10.3) times as likely to have received cervical cancer screening as TMNB patients. Among patients that had received cervical cancer screening, TMNB had a fewer number of screenings than cisgender women (2.5 vs. 3.3 screening visits; P<0.0001).

Conclusions: Despite being at risk, TMNB patients are less likely to be screened for cervical cancer than cisgender women. Further research should focus on more acceptable methods of cervical cancer screening for TMNB to reduce personal barriers to screening. Anticipated changes to national screening systems, with the education of primary care staff and patients, are likely to reach TMNB patients currently missed when they change their gender in medical records.

SS16 - Partnerships with Nordic registries

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#7283

THE USE OF NORDIC REGISTRIES IN PERFORMING LONG-TERM FOLLOW-UP STUDIES OF EFFICACY AND IMMUNOGENICITY OF THE QUADRIVALENT AND 9-VALENT HUMAN PAPILLOMAVIRUS (HPV) VACCINES

06 - HPV prophylactic vaccines

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Background/Objectives: To provide assurances against the lifetime risk of HPV infection, data from prophylactic HPV vaccine clinical programs must demonstrate durable protection against HPV-mediated disease. Clinical registry databases in the Nordic Region and access to surgical pathology specimens have become key to generating evidence on long-term HPV vaccine effectiveness and protection against HPV-related diseases.

Methods: Long-term follow-up (LTFU) extension studies of clinical trials were designed to evaluate long-term effectiveness of the quadrivalent HPV (qHPV) [NCT00092534] and 9-valent (9v) [NCT02653118] HPV vaccines in women aged 16-26 years with follow-up periods of 10-14 years to date. After informed consent, these women simply received routine healthcare and cervical cancer screening in their communities. Rigorous endpoint evaluation was possible because of virtually 100% ascertainment of clinical data, and assiduous cervical cancer screening. Cervical biopsies and other genital biopsies were also accessible and were adjudicated by a Nordic Pathology Panel. HPV typing was also done to determine HPV endpoint attribution. Participants randomized to placebo in the qHPV vaccine trial who received catch-up qHPV vaccination at the end of the base study were followed during LTFU to evaluate effects of delayed vaccination at a slightly older age. Studies of immunogenicity did require an in-person visit to a clinical study site for venipuncture. To assess the population-level impact and effectiveness of HPV vaccines, seven registry-based surveillance studies, including the Vaccine Impact on Population (VIP) study, provided longitudinal data on the incidence of pre-specified HPV-related diseases from the pre-vaccine era (since 2004) through to the post-vaccine era, since 2007.

Results: Results from the Nordic countries demonstrated that the qHPV and 9vHPV vaccines provided durable effectiveness. During LTFU of participants vaccinated at various ages (16-26 years), no cases of high-grade cervical, vulvar, and vaginal dysplasia or cancer or related to vaccine-targeted HPV types were observed, and vaccine effectiveness was demonstrated in the catch-up qHPV vaccination groups. The VIP study demonstrated significant decreases in high-grade cervical dysplasia, cervical cancer, and vaccine-type HPV prevalence, with no evidence of increased risk-taking behavior or vaccine-related congenital anomalies.

Conclusions: Over 10-14 years post-vaccination, the registries provided valuable data on the continued protection of qHPV and 9vHPV vaccines against HPV-related diseases across studies conducted in the Nordic Region. The presentations in this special session will describe evidence that has been gathered from these studies. Experts from the Nordic Region will discuss these findings and provide updates to ongoing longitudinal studies following HPV vaccination.

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#7191

ASSESSMENT OF LONG-TERM EFFECTIVENESS OF THE QUADRIVALENT AND 9-VALENT HPV VACCINES THROUGH NATIONAL REGISTRIES OF NORDIC COUNTRIES

06 - HPV prophylactic vaccines

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Background/Objectives: Pivotal clinical efficacy trials of the quadrivalent human papillomavirus (qHPV) and 9-valent (9vHPV) vaccines in women were extended to assess long-term effectiveness against HPV-related cervical disease. We report 14 and 12 years (y) follow-up data for women vaccinated with qHPV and 9vHPV vaccines, respectively.

Methods: Pivotal efficacy studies enrolled women 16-26 y; participants from Nordic countries were eligible to continue in long-term follow-up (LTFU) studies (NCT00092534; NCT02653118) to evaluate long-term effectiveness of qHPV and 9vHPV vaccines up to 14 years after vaccination, through national health registries. The primary endpoint was the observed incidence of high-grade cervical dysplasia related to HPV16/18 (qHPV vaccine study) and HPV16/18/31/33/45/52/58 (9vHPV vaccine study). Tissue samples collected during routine cervical cancer screening programs were obtained from regional biobanks for polymerase chain reaction HPV testing and pathology diagnosis adjudication. The primary endpoint was assessed in the per-protocol effectiveness (PPE) population. Incidence of the primary endpoint in the LTFU cohort was compared with the estimated incidence in an unvaccinated cohort of similar age and risk level. A control chart method was used to 1) assess the statistical significance of the observed vaccine effectiveness during the LTFU study as follow-up time accumulates, and 2) detect potential waning of vaccine effectiveness over time, during the LTFU study.

Results: Of 2650 women who received qHPV vaccine, no cases of HPV16/18-related high-grade cervical dysplasia were observed during LTFU in the PPE population (n=2121; 17,526.6 person-y follow-up), indicating a vaccine effectiveness of 100% (95% CI 92.7-100). Among 2029 women who received 9vHPV vaccine, there were no cases of HPV16/18/31/33/45/52/58-related high-grade cervical dysplasia during LTFU in the PPE population (n=1628; 10,396.2 person-y follow-up), indicating a vaccine effectiveness of 100% (95% CI 91.9-100). Statistically significant vaccine effectiveness greater than 90% was demonstrated through 12 years post-vaccination dose 3 for the qHPV vaccine and 10 years post-vaccination dose 3 for the 9vHPV vaccine. Although not statistically significant, the finding of vaccine effectiveness greater than 90% extended from 12 to 14 years for qHPV vaccine and 10 to 12 years post-vaccination dose 3 for 9vHPV vaccine, respectively.

Conclusions: The qHPV vaccine provides continued protection through at least 12 years following vaccination with a trend toward continued effectiveness for up to 14 years. The 9vHPV vaccine provides continued protection through at least 10 years following vaccination with a trend toward continued effectiveness for up to 12 years.

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#7282

POPULATION IMPACT AND REAL-WORLD EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION IN DENMARK

06 - HPV prophylactic vaccines

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Background/Objectives: Worldwide, the overall burden of cancers attributable to HPV is substantial, and it is estimated that around 630,000 new cases occur every year. Results from the well-controlled randomized clinical trials have shown high efficacy of the HPV vaccines against genital warts and high-grade cervical, and non-cervical anogenital endpoints. In Denmark, HPV vaccination has been part of the free-of-charge childhood vaccination program provided to 12-year-old girls since January 2009, with a first free-of-charge catch-up vaccination program offered to girls aged 13-15 years in 2008 and a second catch-up vaccination program initiated in August 2012 covering women up to age 27 years. The aim was to assess the population impact and real-world effectiveness of HPV vaccination against cervical, vulvar, vaginal, and anal high-grade lesions.

Methods: The study cohort included all women aged 17-30 years and living in Denmark between October 2006 and December 2019. Individual-level information on exposure, outcomes, and covariates was retrieved from nationwide registries. The women were followed from October 2006 or from their 17th birthday, whichever came last, and until the first occurrence of either outcome (cervical cancer and non-cervical anogenital high-grade squamous intraepithelial lesions (HSIL) and cancer), death, emigration, or end of follow-up, whichever came first. Women were considered vaccinated after the first dose and classified according to age at vaccination.

Results: The incidence rate ratios of cervical cancer were 0.14 (95% CI 0.04-0.53) and 0.32 (95% CI 0.08-1.28), respectively, for women vaccinated at ages 16 years and younger or 17-19 years compared with unvaccinated women. For non-cervical lesions, the adjusted hazard ratio (HR) was reduced for both vulvar (HR 0.22; 95% CI 0.13-0.38), vaginal (HR 0.16; 95% CI 0.04-0.55), and anal HSIL or worse (HR 0.30; 95% CI 0.10-0.87) for women vaccinated at age 16 years or younger compared with unvaccinated women.

Conclusions: Real-world results now document that HPV vaccination at a younger age is associated with substantially reduced risk of cervical cancer and vulvar, vaginal, and anal HSIL or worse, in the general population.

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#6569

PUBLIC HEALTH IMPACT AND COST-EFFECTIVENESS OF SWITCHING FROM BIVALENT TO NONAVALENT VACCINE FOR HUMAN PAPILLOMAVIRUS IN NORWAY: INCORPORATING THE FULL HEALTH IMPACT OF ALL HPV-RELATED DISEASES

35 - Economics and modelling

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Background/Objectives: In this study we aimed to estimate the public health impact and cost-effectiveness of a potential switch from a bivalent to a nonavalent human papillomavirus (HPV) vaccination program in Norway, accounting for all vaccine-preventable HPV-related diseases and in the context of the latest Norwegian cervical cancer screening program.

Methods: We adapted a well-established dynamic transmission model of HPV natural history infection and related diseases to the Norway setting. Most specifically, the model was calibrated and parametrized using Norway's latest epidemiological and sociodemographic data. We determined the number of cases of HPV-related diseases and deaths, as well as the economic burden of HPV-related diseases under the current standard of care conditions of bivalent and nonavalent vaccinations of girls and boys aged 12 years. The model's time horizon was 100 years. Costs and life-years were discounted at 4% in the first 39 years, then at 3% for years 40 to 75, and at 2% for the last 25 years of the model's time horizon.

Results: Compared to bivalent vaccination, nonavalent vaccination averted an additional 4,357 cases of HPV-related cancers, 421,925 cases of genital warts, 543 cases of recurrent respiratory papillomatosis (RRP), and 1,044 HPV-related deaths over a 100-year time horizon. Total costs were higher for the nonavalent strategy (10.5 billion NOK [€1.03 billion]) compared to the bivalent strategy (9.3-9.4 billion NOK [€915-925 million]). Although a switch to nonavalent vaccination had a higher vaccination cost (4.4 billion NOK [€433 million] vs. 2.7 billion NOK [€266 million] for bivalent vaccination), it resulted in a savings of 627-694 million NOK [€62-68 million] in treatment costs. A switch to nonavalent vaccination demonstrated an incremental cost-effectiveness ratio of 102,500 NOK (€10,086) per QALY versus bivalent vaccination.

Conclusions: Using a model that incorporated the full range of HPV-related diseases, and the latest cervical cancer screening practices, we found that switching from bivalent to nonavalent vaccination would be cost-effective in Norway under the proposed willingness-to-pay threshold for low-severity disease.

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#7189

EVEN FASTER CERVICAL CANCER ELIMINATION IN SWEDEN: CONCOMITANT HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AND HPV SCREENING + RISK-STRATIFIED CERVICAL SCREENING

06 - HPV prophylactic vaccines

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Background/Objectives: HPV vaccination and cervical screening are key to eliminating cervical cancer. Vaccination builds population immunity as vaccinated children mature into adults. Cervical cancer elimination involves eradicating incident HPV infections and screening the entire population for HPV. To achieve elimination, incident infections should be prevented through vaccination in birth cohorts still transmitting HPV. By identifying all prevalent HPV cases through a one-time all-inclusive HPV screening campaign, including long-term non-attenders, HPV and cervical cancer elimination can be achieved.

Methods: As part of a nationwide implementation study (NCT04910802), women born between 1994-1999 received personal invitations for concomitant 9vHPV vaccination and HPV screening. The primary endpoint was HPV prevalence, assessed at baseline and at 3 years. Dynamic transmission modeling was used to predict the impact on the wider population. Also initiated was a nationwide trial of risk-stratified cervical screening to improve screening participation for women at higher risk of cervical cancer (NCT04061967). Women identified through the Swedish Cervical Screening Registry with no previous cervical screening, or a history of screening indicating high risk, were personally invited to order a free HPV self-sampling kit by text message or letter. Women positive for high-risk HPV were referred to a regional gynecologist for diagnostic workup.

Results: More than 85,000 women have been invited to enroll in the HPV vaccination and screening study. Results from the first 22,500 women indicate that ~28% were HPV-positive. HPV genotyping found a strong decline of HPV16 and 18 in birth cohorts previously offered vaccination, but no decline for HPV types not targeted by vaccines. Dynamic transmission modeling predicted that the trial could reduce the incidence of high-risk HPV infections among the 1994-1998 cohorts by 64-69% in 3 years. In the risk-stratified screening study, from 2019-2021 we identified 28,689 resident women with either no previous cervical screening or a history of screening indicating high risk. Of these, 2,853 (10.0%) ordered a self-sampling kit and returned a sample for testing. There was low participation among never-attending women (2.7%), but up to 22.5% were tested in other high-risk groups. Repeat invitations modestly increased participation. The highest risk HPV types were detected in 8.3% of samples (238/2853) and 158 women had a cervical biopsy. High-grade cervical intraepithelial neoplasia or worse in histopathology was detected in 36/158 women (22.8%).

Conclusions: The present report describes the first real-life nationwide and population-based implementation of the strategy combining HPV vaccination and HPV screening for faster cervical cancer elimination. We have demonstrated the feasibility of this approach, validated transmission model projections, and obtained power estimates. It is currently being run nationwide, targeting all women born between 1994 -1999 in Sweden (>350,000). For the risk-stratified screening study, we have shown that identification and targeting of women with a high risk of cervical cancer is feasible and that personal invitations to order HPV self-sampling kits resulted in improved participation rates. Approximately 90,000 women are now being contacted yearly. Further efforts are directed to improve the precision of the risk-stratification algorithm, to improve participant convenience, and to ensure that screen-positive women are followed-up.

HN02 - HPV and Head & Neck Forum - Epidemiology and prevention of HPV-OPC

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#7848

Trends in incidence rates of head and neck squamous cell carcinomas in Costa Rica, with a special focus on Human Papillomavirus-related and -unrelated cancers

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Limited data exists on head and neck cancer (HNC) incidence trends in Costa Rica. No investigations on the epidemiology of potentially HPV-related and -unrelated HNCs have been done. We examined the age-standardized incidence rates (ASIRs) and trends of HNCs, comparing potentially HPV-related and -unrelated cases.

Methods: We obtained all available HNC cases for the period 2006-2015 from the National Cancer Registry of Costa Rica and the population estimates from the National Institute of Statistics and Census of Costa Rica. The analysis was restricted to invasive squamous cell carcinomas (SCCs) (n=1577). Age-standardized incidence rates (ASIRs) and trends were calculated using SEER*stat software and the Joinpoint regression analysis program.

Results: The overall ASIR was 34.02/1,000,000 person-years; 95% CI 32.36, 35.75. Laryngeal cancer was the most common cancer site followed by oral cavity and oropharynx. The incidence for all HNSCCs non-significantly declined (APC= -3.20; 95% CI -6.38,0.09). A significant decline in the incidence of nasopharyngeal cancer (APC= -5.86% per year; 95% CI -10.79, -0.66) and laryngeal cancer (APC= -5.41% per year; -9.19,1.47) was observed. The incidence trends for hypopharyngeal, oropharyngeal, and oral cavity cancers remained stable over time. Categorizing HNSCCs by their potential relatedness to HPV infection revealed an upward trend in potentially HPV-related cases, and a downward trend in HPV-unrelated cases; with a marginally significant difference in trends (p for parallelism = 0.061).

Conclusions: HNCs are uncommon in Costa Rica and decreased over time. We observed a divergent pattern of decreasing HPV-unrelated with increasing potentially HPV-related HNCs. Additional research is needed to understand the role of HPV in HNCs in Costa Rica. To assess this, a study is currently in progress to determine the HPV-attributable fraction in HNCs by retrieving and analyzing tumor blocks for oncogenic viral activity. This analysis could provide valuable data to inform prevention strategies, including enhancements to the current HPV vaccination program in the country.

AI02 - HPV and AI Forum - Part II-B - AI and HPV related neoplasia - Prediction models, experiences and perspectives

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#7771

UNCERTAINTY QUANTIFICATION IN AI-BASED PREDICTION MODELS AND POTENTIAL FOR CLINICAL DECISION MAKING

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: Artificial intelligence (AI)-based clinical decision support tools have made considerable advances in this field in recent decades. Although such tools are intended to support clinicians in making decisions under uncertainty, rarely do they provide any uncertainty measures on their own outputs. Moreover, expert clinicians may have experiential knowledge that is not fully reflected in the data used for developing these tools. However, attempts are rarely made to integrate this valuable prior knowledge into AI-based decision-support tools. These two shortcomings, rightfully, have led to hesitancy in the adoption of AI-based tools in clinical practice. This presentation will showcase methods to quantify uncertainty and integrate external expert knowledge into deep learning models using examples from the field of oral lesion identification from intra-oral images.

Methods: Methods: We used intra-oral images compiled by an oral pathologist as part of the routine clinical examination of patients with oral lesions and as part of their electronic health records. The ground truth labels are obtained from pathology reports following the gold-standard diagnosis technique of biopsy or expert clinician's diagnosis. The total dataset contains 12,865 images of 66 different oral lesions across 6000 unique patients. Model: Efficientnet-b5 model, pre-trained on ImageNet, was used as the backbone of the model. Two approaches were compared: i) Evidencial Deep Learning (EDL), which relies on the Dempster-Shafer Theory of Evidence and estimates the parameters of a Dirichlet distribution over the types of oral lesions. ii) MC-DropConnect (MCDC): is an approximate Bayesian approach that can produce samples from the posterior predictive distribution of oral lesion types given an image. Metrics: We adapted the Efficientnet-b5 architecture to each approach and evaluated the metrics of accuracy(F1-score), discrimination (AUC), calibration, and epistemic and aleatoric uncertainty levels between the approaches. The potential impact on clinical decision-making was assessed using decision curve analysis.

Results: Results: The average F1-score of the EDL model was 71.4% compared to 69.7% for the MCDC. Interestingly, the EDL approach showed marginally better accuracy in the majority of the oral lesion types tested. Both models showed similar discriminatory power (AUC=0.94 and 0.92 for MCDC and EDL models, respectively). However, the EDL approach produces better-calibrated probability estimates with expected calibration errors lower than the MCDC.

Conclusions: Conclusion: Our study shows two approaches to uncertainty-aware DL model for oral lesion diagnosis using intra-oral images. The performance of both models was comparable. However, the EDL model has the added advantage of producing better-calibrated predictions and uncertainty estimation without the need for multiple forward passes compared to the MC-DropConnect approach.

AI03 - HPV and AI Forum - Part III - Submitted papers

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#7132

Moving Towards More Personalised Cervical Cancer Screening: Determining Differences in the Risk of CIN2+ by Age and HPV-type in Norway

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: More and more countries are initiating HPV based screening. Many countries have started to include younger women (below 30 years of age) in the screening. The carcinogenicity of the various HPV types is well known, but how screening age affects the probability of developing cancer and precancer, and how to take age into account in the algorithms for following up of test positives, is not well established. In this study we develop a model for predicting cervical intraepithelial neoplasms (CIN) grade 2 or worse (CIN2+) based on type-specific primary HPV testing along with screening age.

Methods: We used a retrospective cohort of 4125 women tested for 14 high-risk HPV (hrHPV) types using the Luminex technology on liquid-based cytology samples (1). The women were included between 2006 and 2013 and followed up for CIN2+ until 2020. Age at screening was 18-50 years, with half of the women being below 25 years of age. Risk of CIN2+ was modelled by the Cox proportional hazards model using age as running time. Each of the 14 hrHPV types were included as covariates. Screening age was also included, along with interaction terms for HPV type and screening age. Model selection was performed by cross-validation using C-index as performance measure.

Results: There was a significant interaction with age of screening for several carcinogenic HPV types. We hypothesize two reasons for this screening age dependency: (I) greater ability of HPV clearance for younger women, and (II) increased rate of persistent infections by age.

Conclusions: We have built a model for predicting high-grade pre-cancerous cervical lesions based on type-specific HPV testing, taking age of screening into account. The model can be used to obtain improved and more personalized algorithms for following-up of HPV positive women from cervical cancer screening.

References: 1. Dillner J, Nygård M, Munk C, Hortlund M, Hansen BT, Lagheden C, Liaw KL, Kjaer SK. Decline of HPV infections in Scandinavian cervical screening populations after introduction of HPV vaccination programs. Vaccine. 2018 Jun 18;36(26):3820-3829. doi: 10.1016/j.vaccine.2018.05.019. Epub 2018 May 31. PMID: 29778519.

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#6740

MACHINE LEARNING MODEL FOR CERVICAL CANCER RISK PREDICTION

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: Most (>80%) of Swedish women consistently participate in cervical screening and typically receive normal results, resulting in a very low cervical cancer risk of less than 1/100,000 person-years. However, Sweden's current cervical cancer rate stands at over 11/100,000 women-years. The majority of cervical cancer cases come from a small, readily definable high-risk group with either long-term non-attendance or a history of inadequate screening with abnormal screening results.(1) We aimed to better understand why the cervical cancer rate is so high in presence of very high population attendance of screening. We also wished to explore the predictive values of machine learning (ML) to identify cervical cancer risks and predict which new screening efforts that are likely to have the greatest benefit. Risk-stratified screening targeting only the women who really need screening has the potential to both increase benefits with more intense screening of high risk women and reduce harms of unnecessary screening. We used the Swedish national cervical screening registry (NKCx), which records all screening-related data at the individual level (including invitations, HPV tests, cytology and histology with 100% national coverage).(2) Previously we identified 6 different groups of women at high risk and launched a nationwide trial that once per year invites all women in these groups to self-sampling for HPV screening. We now aim to develop a machine learning method that considers all available data and will predict the risk for developing cancer, based on the data in the screening registry.

Methods: This study utilizes the NKCx, with individual-level data from 5.1 million women aged 23 to 85. The dataset comprises patient ID, age, HPV test results, cytology outcomes, histology results and invitation details. All women in the country were included. Follow-up was censored at death, emigration or diagnosis of invasive cervical cancer. We trained a gradient boost algorithm, combining learners to build robust models less sensitive to outliers, to predict cancer development, assigning endpoints based on histology (if cancer was present). If a women had cancer as diagnosis, all data preceding the cancer by more than 6 months were used to train the algorithm, in comparison to all women in the country without cervical cancer. The model is being trained with 75% of the data and tested using cross-validation, using sets with similar class proportions. Performance is evaluated using metrics like weighted accuracy, sensitivity, specificity, and AUC to determine the most predictive features for cancer.

Results: Not available yet

Conclusions: Artificial intelligence is a potentially suitable solution for identifying women at high risk for developing cervical cancer. Identification can serve as input for risk stratified screening approaches to achieve a faster cervical cancer elimination.

References: 1- Arroyo Mühr LS, Wang J, Hassan SS, et al. A Nationwide Trial of Risk-Stratified Cervical Screening for Faster Cervical Cancer Elimination. Pre-print available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4555193, accessed on 2023-10-10. 2- Swedish national cervical screening register. Available at https://nkcx.se/, accessed on 2023-10-10.

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#6730

AUTOMATED EVALUATION OF P16/KI67 DUAL STAIN CYTOLOGY AS AN ARTIFICIAL INTELLIGENCE-BASED BIOMARKER FOR DETECTION OF CERVICAL INTRAEPITHELIAL NEOPLASIA OF GRADE 2 OR WORSE IN OLDER HPV-POSITIVE WOMEN IN CERVICAL CANCER SCREENING - A CROSS SECTIONAL STUDY

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: HPV-based cervical screening has better performance than cytology-based screening but relies on additional triage to limit unnecessary colposcopy referrals of HPV-positive women without precancer. Yet, cytology triage has limited sensitivity and is difficult to interpret in postmenopausal women due to atrophic changes. This highlights the need for more disease-specific biomarkers like the p16/Ki67 dual immunostaining cytology test (DS). Manual DS evaluation has shown better performance for triage of HPV-positve women compared to cytology. To match or improve the performance of manual DS, the artificial intelligence-based CYTOREADER system with automated scanning and evaluation of DS slides (automated DS) was developed and showed improved performance compared to manual DS in initial studies. Here, we compared the clinical performance of DS triage testing vs cytology and automated and assisted DS vs manual DS evaluation for the detection of Cervical Intraepithelial Neoplasia, CIN, grade 2 or worse (CIN2+) among older postmenopausal HPV-positive women.

Methods: We conducted a paired cross-sectional study including cytology and DS slides from HPV-positive women aged 45-69 (median age: 68 yrs) in 2019. DS was performed using the CINtec® PLUS assay. Two cytotechnologists interpreted cytology and DS slides. A slide was scored manual DS positive if ≥ 1 cervical epithelial cell stain was positive for both p16 and Ki67. Automated DS evaluation used a validated algorithm to quantify the number of DS-positive cells above a likelihood threshold (a ≥ 2 DS cells threshold was used). The assisted DS approach provided the cytotechnicians with an overview of the tiles with possible DS-positive cells and the slide was then scored positive or negative by the technician (threshold: ≥ 1 DS cell was used). Histology was grouped as infCIN2 (normal and CIN1) and CIN2+ (CIN2, CIN3/AIS, and cancer) after a follow-up length of 25-33 months. The McNemar $\chi 2$ (McN) test was used to compare differences in sensitivity and specificity between the triage tests.

Results: In total, 46 and 348 women were diagnosed with CIN2+(11.7%) and 87.0%) but only when using assisted DS evaluation, the difference reached statistical significance (73.9% vs 91.3%, pMcN=0.02). In contrast, cytology (90.2%) had significantly higher specificity than manual (62.1%, pMcNinf0.01), assisted DS (47.1%, pMcNinf0.01), and automated DS (67.5%, pMcNinf0.01). Compared to manual DS, automated DS had equivalent sensitivity (87.0%) to detect CIN2+ and significantly higher specificity (67.5% vs 62.1%, pMcN=0.03, respectively). Compared to manual DS, assisted DS had similar sensitivity (91.3% vs 87.0%, pMcN=0.50, respectively) and significantly lower specificity (47.1 vs 62.1%, pMcNinf0.01, respectively).

Conclusions: Our results indicate that the sensitivity of triage testing in older HPV-positive postmenopausal women can be increased by using DS evaluation compared to cytology. Automated DS has higher specificity compared to manual DS and provides a good balance between ensuring detection of precancer while minimizing unnecessary colposcopy referral in this population. Going forward, the performance of manual and automated p16/Ki67 DS triage will be investigated in larger upcoming studies in women aged 50-69 years.

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#6950

RISK STRATIFIED MANAGEMENT OF CERVICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS BASED ON MACHINE LEARNING

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: The recommended treatment of colposcopically directed biopsy (CDB) confirmed cervical high-grade squamous intraepithelial lesions (HSIL) is conization. However, the pathology diagnosis concordance rate for CDB diagnosed HSIL and conization is 64-85%, with 2-13% of patients upgrading to invasive cervical cancer and 14-26% downgrading to low-grade squamous intraepithelial lesions (LSIL) or below. Therefore, we aim to manage risk stratification for cervical HSIL patients based on machine learning predictive model.

Methods: 1. This retrospective study included patients who visited Obstetrics and Gynecology Hospital of Fudan University China from January 1, 2019, to December 31, 2019, and were diagnosed with cervical HSIL by CDB and subsequently underwent conization. Demographic data, laboratory findings, colposcopy descriptions, and pathological results were collected from medical records. Patients were categorized into three groups according to pathological results after conization: LSIL- group, HSIL group, and cervical cancer group. 2. Univariate and multivariate analysis were conducted to obtain the independent risk factors for pathological changes in cervical HSIL patients. 3. Machine learning prediction models were established and evaluated, subsequently verified in external testing data.

Results: 1. A total of 1585 patients were enrolled, among which 373 (23.5%) were downgrade to LSIL- after conization, 1147 (72.4%) remained HSIL, and 65 (4.1%) were upgrade to cervical cancer. 2. The results of univariate and multivariate analysis showed that a 2% decrease in the incidence of pathologic downgrade was found for each additional year of age and each 1% increase in lesion area. Patients with cytology >LSIL (OR=0.33, 95%CI: 0.21-0.52), HPV infection (OR=0.33, 95%CI: 0.14-0.81), HPV 33 infection (OR=0.37, 95%CI: 0.18-0.78), coarse punctate vessels on colposcopy examination (OR=0.14, 95%CI: 0.06-0.32), and HSIL lesions in endocervical canal(OR=0.48, 95%CI: 0.30-0.76) were less likely to experience pathologic downgrading after conization. Compared to patients with colposcopy impression of LSIL or inflammation, patients with HSIL impression (OR=0.02, 95%CI: 0.01-0.03) were less likely to experience pathologic downgrading. The independent risk factors of pathological upgrading to cervical cancer after conization including: age (OR=1.08, 95%CI: 1.04-1.12), HPV16 infection (OR=4.07, 95%CI: 1.70-9.78), the presence of coarse punctate vessels during colposcopy examination (OR=2.21, 95%CI: 1.08-4.50), the presence of atypical vessels (OR=6.87, 95%CI: 2.81-16.83), and the presence of HSIL lesions in cervical canal (OR=2.91, 95%CI: 1.46-5.77). 3. In 6 machine learning prediction models, the BP neural network model demonstrated highest and most uniform predictive performance in the LSIL- group, HSIL group, and cervical cancer group, with AUCs of 0.90, 0.84, and 0.69, respectively, sensitivities of 0.74, 0.84 and 0.42, specificities of 0.90, 0.71 and 0.95. In the external testing set, the BP neural network model showed a higher predictive performance than the logistic regression model, with the overall AUC of 0.91. Thus, a web-based prediction tool (http://115.29.79.17:8082/) was developed and a software copyright "AI Risk Prediction Model for Cervical Precancerous L

Conclusions: BP neural network prediction model has better predictive performance and can be used for risk stratification of CDB diagnosed HSIL patients.

ROC curve of BP neural network prediction model

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#6902

CERVIXGUIDE - A NEW ARTIFICIAL INTELIGENCE TOOL

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: Artificial Intelligence (AI) refers to the simulation of human intelligence in computer systems, allowing them to perform tasks that typically require human intelligence, such as understanding natural language, recognizing patterns, solving complex problems, and making decisions. In the field of healthcare, AI has made significant advancements and offers various applications aimed at improving patient care, diagnosis, treatment, and the overall efficiency of healthcare systems. Language models are at the forefront of cutting-edge AI research, revolutionizing the way machines understand and generate human language. These models have emerged as a transformative force in AI, enabling a wide array of natural language processing tasks, from translation and chatbots to text generation. Language models are sophisticated AI systems that are trained on vast text datasets. They employ deep learning techniques, particularly deep neural networks, to encode and decode the complexities of human language. These models are designed to comprehend and generate text that exhibits human-like fluency and coherence. Health organizations worldwide publish clinical guidelines for cervical cancer screening, follow-up, and treatment. These guidelines offer evidence-based guidance for healthcare professionals. In Portugal, in 2023, it was published a Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests. The objective of this project was to create a conversational application, CervixGuide (Cervical Cancer Guidelines Language Model), using language models, which understands the Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests by the Portuguese Section of Colposcopy and Lower Genital Tract Pathology (SPCPTGI).

Methods: CervixGuide was programmed to transform the Portuguese Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests by the SPCPTGI, into a shared knowledge matrix with the language model, making it the sole source of information. The language models used were trained in the Portuguese language. CervixGuide is accessible through a website, enabling access on mobile devices.

Results: CervixGuide is an application for professional use that contribute to expanding the reach of a specific digital content. The model only provides responses based on the Portuguese Consensus and any question on different topics will not be answered. To increase confidence and robustness of CervixGuide´s information, it is possible to provide feedback on the accuracy/appropriateness of responses to clinical scenarios. The use of a single source of information eliminates biases.

Conclusions: Language models have become an essential tool for AI researchers and developers, driving innovation and experimentation in various AI applications. The implementation of AI can be crucial in providing better healthcare to women in various areas, including cervical cancer screening.

References: 1) Dhombres, Ferdinand, et al. "Contributions of artificial intelligence reported in obstetrics and gynecology journals: systematic review." Journal of medical Internet research 24.4 (2022): e35465. 2) Iftikhar, Pulwasha, et al. "Artificial intelligence: a new paradigm in obstetrics and gynecology research and clinical practice." Cureus 12.2 (2020). 3) Malani SN 4th, Shrivastava D, Raka MS. "A Comprehensive Review of the Role of Artificial Intelligence in Obstetrics and Gynecology". Cureus. 2023 Feb 12;15(2):e34891. 4) Nori, Harsha, et al. "Capabilities of gpt-4 on medical challenge problems." arXiv preprint arXiv:2303.13375 (2023). 5) Pedro A, et al. "Orientações de Consenso para a Abordagem dos Resultados Alterados nos Testes de Rastreio do Cancro do Colo do Útero pela SPCPTGI [Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests by the SPCPTGI]". Acta Med Port. 2023 Apr 3;36(4):285-295. 6) Seval, Mehmet Murat, and Bulut Varlı. "Current developments in artificial intelligence from obstetrics and gynecology to urogynecology." Frontiers in Medicine 10 (2023): 1098205. 7) Touvron, Hugo, et al. "Llama: Open and efficient foundation language models." arXiv preprint arXiv:2302.13971 (2023).

Young Scientists Award & Welcome Ceremony

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#6743

LOCALISED TOPICAL MICROWAVING REVERSES HUMAN PAPILLOMAVIRUS (HPV) INDUCED PROLIFERATION AND IMMORTALISATION IN VITRO IN HPV-POSITIVE 3D EPITHELIAL RAFT TISSUES

20 - New technologies

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Background/Objectives: Hyperthermia has been used as an adjuvant to cancer therapies1 while thermal coagulation is recommended by the WHO to treat cervical intraepithelial neoplasia (CIN) and cancer in low and middle-income countries. Microwave-induced hyperthermia has been shown to give a clearance of 75.9% of HPV-positive verrucas2 and >90% of actinic keratoses3, which can also be HPV-associated, suggesting that microwave heating could be a novel therapy against HPV-associated anogenital lesions. We characterised the molecular effects of microwave treatment on in vitro cultured HPV-positive 3D raft tissues representing CIN or cervical cancer4.

Methods: A hand-held medical device delivering microwaves through a 7mm contact site was used to treat HPV16-positive SiHa cervical cancer cells and HPV16-infected normal immortalized keratinocytes (NIKS16) grown as 3D tissue cultures. Immunohistochemistry and immunofluorescence microscopy were used to determine the molecular effects of microwave treatment. RT-qPCR was used to analyse changes at the transcriptional level of expression of the E6/E7 oncoproteins and late E4 and L1 HPV genes. Luminex assays were used to analyse changes in cytokine expression.

Results: Hyperthermia was confirmed by upregulated HSP70 in the microwave-treated tissues, and cell ablation was precise at the treatment site. Tissue structure was undisturbed away from the treatment site, but apoptosis and autophagy markers were induced. In treated SiHa cells, the levels of p53 and Rb were upregulated with a corresponding decrease in HPV16 E6/E7 oncoprotein expression. In HPV-positive keratinocytes, viral late protein expression was reduced. No tissue regrowth was detected up to 72 hours post-treatment. Cell proliferation decreased in a sustained manner in all tissues and in NIKS16, there was a corresponding increase in differentiation. Treatment resulted in an upregulation of several cytokines, involved in innate immunity, in NIKS16 tissues. These data show that microwave treatment can reverse the growth stimulatory and de-differentiation effects of HPV infection and promote innate immunity.

Conclusions: Microwaves can ablate tissue precisely, inhibit expression of the viral proteins and stimulate natural cellular apoptosis and innate immunity. This novel approach could be a promising new, less painful treatment for the treatment of HPV-infected anogenital lesions.

References: 1: DOI: 10.3109/02656736.2014.968640 2: DOI: 10.1684/ejd.2017.3086 3: DOI: 10.1111/bjd.18935 4: DOI: 10.1016/j.ebiom.2023.104577

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#6751

EVIDENCE OF DECREASED LONG-TERM RISK OF CERVICAL PRE-CANCER AFTER NEGATIVE PRIMARY HPV SCREENS COMPARED TO NEGATIVE CYTOLOGY SCREENS IN A LONGITUDINAL COHORT STUDY

10 - HPV screening

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Background/Objectives: To meet the World Health Organization goal for the elimination of cervical cancer, many jurisdictions are implementing primary HPV screening. HPV screening is more sensitive than cytology, allowing for extended intervals between negative screens. Currently, HPV screening is most commonly recommended at 5-year intervals, but it is possible that this interval could be safely further extended to reduce the burden on both the health system and those who are eligible to be screened for cervical cancer. This study examined the long-term risk of cervical precancer or cancer after primary HPV screening compared to cytology.

Methods: The HPV FOCAL randomized controlled trial (British Columbia (BC), Canada; N = 25,223) compared primary HPV screening to cytology for cervical cancer screening. The FOCAL-DECADE longitudinal cohort was created by linking data from HPV FOCAL to BC's provincial cervical cancer screening program, which uses cytology to screen for cervical cancer. Participants who received one (HPV1 cohort, N = 5,546) or two (HPV2 cohort, N = 6,624) negative HPV test result(s) in HPV FOCAL were compared to a cohort of participants extracted from the provincial screening program who had one (BCS1 cohort, N = 782,297) or two (BCS2 cohort, N = 673,778) normal cytology result(s). All participants were followed through the provincial registry for 14 years. We measured the long-term risk of cervical precancer or cancer (CIN2+) in HPV-screened cohorts compared to cytology-screened cohorts.

Results: The cumulative risk of CIN2+ was 3.2/1000 (95% CI: 1.6 to 4.7) in HPV1 and 2.7/1000 (CI: 1.2 to 4.2) in HPV2 after 8 years. This was comparable to the risk in the cytology cohorts after 3 years (BCS1: 3.3/1000, [CI: 3.1 to 3.4]; BCS2: 2.5, [CI: 2.4 to 2.6]). The cumulative risk of CIN2+ after 10 years was low in HPV cohorts (HPV1: 4.7/1000, [CI: 2.6 to 6.7]; HPV2: 3.9, [CI: 1.1 to 6.6]), and remained low up to 14 years.

Conclusions: Risk of CIN2+ eight years after negative screen results in HPV cohorts was comparable to risk after 3 years in cytology cohorts (the screening interval in BC, thus considered the benchmark for acceptable risk). These findings suggest that primary HPV screening intervals could be extended beyond the current five-year recommendation.

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#7104

Human Papillomavirus Circulating Tumor DNA Characterization for Risk Stratification in Cervix Cancer

15 - Molecular markers

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Background/Objectives: Cervix cancer, predominantly caused by human papillomavirus (HPV), has heterogeneous outcomes that are difficult to predict based on clinical features alone, highlighting the unmet need for improved biomarkers for risk stratification. Patients with locally advanced cancer have 5-year progression-free survival (PFS) of 60%. HPV circulating tumor DNA (ctDNA) has prognostic value after completion of treatment, but its role at diagnosis prior to treatment is less defined. We hypothesized that pre-treatment HPV ctDNA levels, as well as the presence of viral integration in ctDNA prior to treatment can serve as prognostic markers and may identify patients at higher risk of disease recurrence who may benefit from treatment escalation.

Methods: Plasma cell-free DNA was collected pre-treatment from patients with either locally advanced (stage IB-IVA) (n=70) or metastatic (n=23) HPV-associated cervix cancer. Whole viral genome sequencing was performed following hybrid capture. The primary endpoint, PFS, was analyzed using the Kaplan-Meier method and log rank tests. HPV ctDNA levels were expressed as copies/mL plasma. Integration sites of HPV in the host genome were detected by SearcHPV. Genes within 100kb from each site were analyzed using DepMap CRISPR-Cas9 screening datasets, where the proportion of genes with a reduction in cell survival upon knockdown (median CHRONOS<0) was calculated within 16 cervix cancer cell lines and compared to 1,000 random permutations.

Results: Baseline HPV ctDNA levels were significantly higher in metastatic patients (median 299.4 copies/mL) than locally advanced patients (median 168.7 copies/mL) (p=0.009). Among locally advanced patients, 34% (n=24) recurred. Baseline HPV ctDNA levels trended higher in locally advanced patients who recurred than those who did not (p=0.1). Metastatic patients had higher baseline HPV ctDNA levels than those without recurrence (p=0.007). HPV integration was more common in metastatic patients than locally advanced patients (p=0.04). Among patients with detectable HPV integration, metastatic patients had more host genome sites than locally advanced non-recurrent patients (p<0.001), but similar to recurrent patients (p=0.2). Locally advanced patients with detectable HPV integration (2-year PFS 54%), with high confidence integration sites (2-year PFS 48%), or with >2 integration sites (2-year PFS 29%) displayed worse prognosis than those with undetectable integration (2-year PFS 76%). In all patients, we detected 230 integration sites, with no repeat sites. Within 100kb of all integration sites, 282 genes were identified, including those in HPV infection and cancer pathways (i.e., JAG1, MAPK3). 168 of the 217 genes (77%) included in the DepMap screen exhibit oncogenic potential through their knockdown in cervix cancer cell lines (p<0.001).

Conclusions: We found that locally advanced cervix cancer patients who relapsed displayed HPV ctDNA levels and HPV-host integration patterns similar to metastatic patients. Evidence of viral integration detected from HPV ctDNA was associated with significantly reduced survival. Genes in the vicinity of integration sites have potential roles in HPV infection and cancer pathways, with a notable subset demonstrating oncogenic potential. Altogether, this work suggests that quantitative and qualitative features of HPV ctDNA from baseline plasma could aid in risk stratification of locally advanced cervix cancer and guide therapy decisions.

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#7108

HUMAN PAPILLOMAVIRUS VACCINATION DECISION-MAKING AMONG ADOLESCENT GIRLS IN JAPAN: A QUALITATIVE STUDY

36 - Advocacy, acceptability and psychology

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Background/Objectives: To prevent cervical cancer, human papillomavirus (HPV) vaccine was introduced in Japan in April 2013 for girls aged 11-16. However, due to public anxiety about adverse events, the government suspended the proactive vaccine recommendations in June 2013. While HPV vaccine was still available during the suspension of the recommendations, the coverage has remained only 1-16% over this decade. Despite the resumption of recommendations in April 2022, a long history of public uncertainty about HPV vaccine is problematic as the success of vaccination ultimately depends on public vaccination decision-making. There is a growing recognition that vaccination decision-making is not necessarily an individual cognitive behaviour - instead it is shaped by interaction with different social groups, such as family members, peers and healthcare workers. However, few past studies in Japan examined the social group environment in which adolescent girls think and decide about HPV vaccination. To address the knowledge gap, this research aims to characterise the social group environment in which girls decide whether to be vaccinated and examines the influence of group dynamics (peer and social norms) on their decisions.

Methods: Focus Group Discussions (FGDs) were conducted with female high school students aged 16-18yrs in three regions of Japan, using a topic guide developed based on the research aims. To characterise the structure of the social group involved in HPV vaccination decision-making, visual mapping was used. Participants were asked to arrange cards on which different types of information sources/key persons were drawn from the circle's centre in order of 1) influence and 2) trust. Thematic analysis was conducted to identify themes in the areas of exploration. In April 2022, an HPV vaccine catch-up program commenced to provide girls aged 17-26, who missed-out on vaccination due to suspension of proactive recommendations, with an opportunity for HPV vaccination. We recruited from this group.

Results: [Preliminary] Seven FGDs with 3-7 girls (33 girls in total) were conducted from February to July 2023, either in person (in school classrooms) or online, depending on the COVID-19 restrictions in each region. Several key themes were identified such as "influence of narratives of peer students who have experienced HPV vaccination" and "inconsistency between trusted and influential information sources". For example, while healthcare professionals were most trusted by the participants, they were less likely to be contacted by girls before girls decided whether to receive HPV vaccine due to the lack of opportunities for communication between them.

Conclusions: [Preliminary] Communication about HPV vaccine should be delivered by leveraging established local trusted entry points (1), so concerns about the vaccine are effectively addressed. Although it is essential to educate parents and schoolteachers, who often communicate with high school girls and are thus influential in their views, it is also necessary to improve the accessibility to healthcare professionals in whom adolescents placed the most trust. Within the overall reproductive health system in the country, more emphasis should be placed on adolescent health to build healthcare workers' capacity for consultation with adolescents, give healthcare facilities financial incentives or let adolescents know about the roles of gynaecologists, so that chances of communication between adolescent girls and healthcare workers can be increased.

References: (1) Larson HJ, Broniatowski DA. Volatility of vaccine confidence. Science. 2021;371(6536):1289-

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#7193

ALTERNATIVE TREATMENT OPTIONS TO SURVEILLANCE FOR PERSISTENT HPV FOLLOWING A POSITIVE RESULT FROM THE CERVICAL SCREENING PROGRAMME: A SYSTEMATIC REVIEW & META-ANALYSIS OF THE LITERATURE

22 - Diagnostic procedures / management

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Background/Objectives: In March 2020, the Scottish Cervical Screening programme changed from cervical cytology testing (test of disease) to high-risk human papillomavirus (hr-HPV) testing (test of risk). This change has effectively led to a "new disease' as women are now aware of having a potentially pre-cancerous virus, which they would have been unaware of previously. While current management involves a "watch and wait' approach and no active treatment, the anxiety associated with having hr-HPV has prompted some women to seek "treatments,' outside the screening programme.

Methods: to identify the treatment options available for women with persistent hr-HPV and/or low-grade cervical intraepithelial neoplasia (CIN), i.e. no greater than CIN 1. to determine the clinical effectiveness of these treatments to clear hr-HPV. We searched MEDLINE, PubMed, EMBASE, Web of Science and the Cochrane Library. We included cohort studies and randomised controlled trials (RCTs) only. Records (n=2135) were screened in Rayyan by two independent reviewers. The ROBINS-I tool (Risk Of Bias In Non-randomised Studies - of Interventions) was used to assess the quality of the non-randomised studies. The ROB-2 tool (Risk Of Bias for randomised trials) was used to assess the quality of the randomised studies.

Results: 18 studies (4 cohort studies and 14 RCTs) met our inclusion criteria. The studies identified several treatment options, including 7 studies with oral medications, 5 with topical medications, 2 with vaccinations, and 3 with non-surgical device treatments. Preliminary analysis of the studies revealed that some therapeutic interventions, including vaginal gels, photodynamic therapy, and some oral medications, may lead to earlier resolution of persistent hr-HPV and regression of low-grade CIN, when compared with natural clearance.

Conclusions: This review can better inform discussion with hr-HPV + women and answer their questions about alternatives to surveillance.

SS20 - Sexual abuse and HPV

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Epidemiology and diagnosis of STIs in children being evaluated for suspected sexual abuse

03 - Epidemiology and natural history

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Background/Objectives: Testing for sexually transmitted infections (STIs) in children presents a number of problems for the practitioner that are not usually faced when testing adults for the same infections. The identification of an STI in a child, in addition to medical implications, can have serious legal implications. The presence of an STI is often used to support the presence or allegations of sexual abuse, and conversely, the identification of an STI in a child will prompt an investigation of possible abuse. The significance of the identification of a sexually transmitted agent in such children as evidence of possible child sexual abuse varies by pathogen.

Methods: This is a review of availalble studies of STIs in this population.

Results: Although the identification of sexually transmissible agents in children beyond the neonatal period suggests sexual abuse, exceptions do occur. Perinatally acquired rectal or vaginal Chlamydia trachomatis infection may persist for 2 to 3 years after birth. Bacterial vaginosis (BV) has been diagnosed for children who have been abused, but its presence alone does not prove sexual abuse. However, postnatally acquired gonorrhea; syphilis; and non-transfusion-acquired and non-perinatally-acquired HIV are usually diagnostic of sexual abuse. Studies of STIs in children have demonstrated significant variability in the prevalence of infection. In many earlier studies, only symptomatic children were tested, which often gave higher prevalences of gonococcal infection than studies that tested all children being evaluated for suspected sexual abuse. Studies of C. trachomatis infection were not done until the 1980s. However, subsequent studies of STIs in sexually abused children have reported low rates of infection. Several large studies of the prevalence of STIs in children being evaluated for suspected sexual abuse have been published since 2005. Several used nucleic acid amplification tests (NAATs) for detection of C. trachomatis and Neisseria gonorrhoeae, but others relied on culture, wet mounts for T. vaginalis. The overall rates of STIs were low, prevalence of N. gonorrhoeae ranged from 0.05 to 3.3%; prevalence of C. trachomatis, 0.5-3.1%; Trichomonas vaginalis, 0.7-5.9%. Criteria for the diagnosis of human papillomavirus (HPV) infection in children, clinical versus detection of HPV DNA, is also not standardized. Most studies have relied on the presence of clinical lesions consistent with genital warts for the diagnosis of HPV infection. The prevalence has been < 5%. The CDC 2021 STI Guidelines stated that presence of anogenital warts in children is suspicious as opposed to diagnostic of sexual abuse.

Conclusions: The low prevalence of STIs in these children has a significant impact on the performance of diagnostic tests, including NAATs. When the prevalence of infection is <5%, even highly sensitive and specific methods such as NAATs can be associated with low positive predictive values and false positive results. The Centers for Disease Control recommended in 2021 that all positive tests for N. gonorrhoeae and C. trachomatis in these children be confirmed. However, this is frequently not done in practice which can lead to adverse social and legal consequences for the child and the family.

References: Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70(No. RR-#4):1-192. Hammerschlag MR, Guillen CD. Medical and legal implications of testing for sexually transmitted infections in children. Clin Microbiol Rev 2010; 23:493-506.

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#7853

OVERVIEW OF CONFUSION AND NEED FOR FURTHER STUDIES

32 - HPV transmission

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Background/Objectives: The sexual transmission of HPV is nothing new. Data continue to show this is the most efficient mode of transmission with documented high transmission rates between couples. The finding of external genital warts (EGW) is not confined to post-pubertal persons. Transmission of HPV DNA between mother and infant has been noted but most studies conclude this transmission is transient. On the other hand, the rare persistent infections of HPV in infants has also been observed but its role in the development of EGW has not.

Methods: Systematic reviews continue to support the diagnosis of child sexual abuse in children older than 3 years of age diagnosed with EGW. Below this age, diagnosis becomes problematic because children are often non-verbal and that contact to the genital area may not be recognized as inappropriate by the child. This session gives us a broad view of the evidence that HPV transmission occurs during perinatal delivery, care-takers and child sexual abuse (CSA).

Results: The importance is that physicians and care-providers recognize that EGW could result from sexual abuse and further investigations are required by experts in this area. The mere discussion of "possible" sexual abuse causes distress in children, parents and the care-provider. On the other hand, false allegations of CSA also have long term detrimental effects on the family and the accused. To make matters more confusing, age of consent varies greatly between countries, hence a diagnosis of EGW in a 11 year old may not be further investigated in a country where sexual consent starts at this age.

Conclusions: This session will conclude with important areas of research including larger, more comprehensive studies of HPV detection in both girls and boys; role of HPV DNA sequencing, protocol development to evaluate HPV in CSA and HPV vaccination at age of EGW/HPV diagnosis.

SS22 - Methylation markers as management tool in anal, vulvar and cervical intraepithelial neoplasms

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METHYLATION IN ANAL NEOPLASIA

17 - Methylation

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Background/Objectives: Currently, all high-grade anal intraepithelial neoplasia (HGAIN) are being treated while only a small subset would progress to cancer. Hence, there is an urgent clinical need for an objective biomarker test to guide HGAIN management and diminish (over)treatment. As methylation is correlated with carcinogenesis, the use of methylation markers holds great potential. In this presentation we provide an overview of the current status of methylation analysis on anal biopsies and the future clinical applications.

Methods: --

Results: --

Conclusions: --

SS19 - Scientific approaches to defining HPV vaccine-induced protective immunity

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L1 ANTIGENS RECOGNIZED BY INFECTION VS VACCINE-INDUCED NEUTRALIZING ANTIBODIES

19 - Serology

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Background/Objectives: HPV vaccines demonstrate excellent efficacy in clinical trials and effectiveness in national HPV vaccination programmes against the most prevalent genotype, HPV16. It is unclear whether the greater protection conferred by vaccine-induced antibodies, compared to natural infection antibodies, is simply due to differences in antibody magnitude or whether there are also important differences in antibody specificity. We explored the contribution of the surface-exposed loops of the major capsid protein to antigenic domains recognized by vaccine and natural infection derived neutralizing antibodies.

Methods: Chimeric non-reactive HPV35 pseudovirus (PsV) incorporating individual (BC, DE, EF, FG, HI) or combined (ALL: BC/DE/EF/FG/HI) loop swaps from susceptible HPV16 PsV were generated, purified by ultracentrifugation and characterized by SDS-PAGE and electron microscopy. Neutralizing antibody data were subjected to hierarchical clustering and outcomes modelled on the HPV16 capsomer crystal model.

Results: The chimeric HPV35ALL PsV incorporating all the HPV16 loops demonstrated similar neutralization susceptibility to vaccine and natural infection antibodies as the reference HPV16 PsV (natural log neutralizing antibody titer ratio: median 1.01; inter-quartile range, 0.99 - 1.03; r = 0.992; n = 62) suggesting that almost the entirety of the neutralizing antibody response targets the external surface exposed loops. Vaccine antibodies exhibited an FG loop preference followed by the EF and HI loops while natural infection antibodies displayed a more diverse pattern, most frequently against the EF loop followed by BC and FG. Both vaccine and natural infection antibodies demonstrated a clear requirement for multiple loops to fully reconstitute their neutralizing antibody capacity. Crystal modelling of these neutralizing antibody patterns suggested natural infection antibodies typically target the outer rim of the capsomer while vaccine antibodies target the central ring around the capsomer lumen, although there was a significant amount of overlap.

Conclusions: Chimeric pseudoviruses are useful tools for probing vaccine and natural infection antibody specificity. These data add to the evidence base for the effectiveness of an important public health intervention.

SS21 - HPV driven cancer among people living with HIV

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#7752

A GLOBAL COMPARISON OF INCIDENCE RATES AND TRENDS IN HPV-RELATED CANCERS AMONG PEOPLE WITH HIV

03 - Epidemiology and natural history

Background/Objectives: People with HIV have a higher risk of HPV-related malignancies, most notably cervical and anal cancers. The risk of HPV-related cancers among people with HIV is driven by a number of factors. For example, the availability of cervical cancer screening and follow-up, HIV-related immunodeficiency, viral suppression of HIV due to effective antiretroviral therapy, prevalence of HPV infection, and the age composition of the HIV population all influence both rates of HPV-related cancers and their trends over time. As a result, there are notable geographic differences in the rates and trends of HPV related cancers over time among people with HIV. This talk will focus on global comparisons of HPV-related cancers occurring among people with HIV.

Methods: N/A

Results: The presenter will give an overview of 1) incidence rates; 2) trends over time, and 3) relative risks compared to the general population for a number of HPV-related cancers across geographic regions. As an example, it has been shown that rates of cervical cancer are notably higher among women with HIV in South Africa than Latin America, North America or Europe, with rates 11-times greater 5 years after antiretroviral therapy initiation (Rohner et al., IJC 2020). Substantial variation in the fraction of anal squamous cell carcinomas occurring among people with HIV has also been reported, with the largest number of cases occurring among men with HIV in the United States (Deshmukh et al. IJC 2023).

Conclusions: The presenter will discuss potential drivers of international differences in HPV-related cancer rates and trends among PWH, as well as the need for cancer prevention among people with HIV.

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#7732

INCIDENCE, TRENDS AND BURDEN OF HPV-RELATED CANCERS IN A HIGH HIV-SETTING: THE SOUTH AFRICAN NATIONAL CANCER REGISTRY

39 - Public health

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Background/Objectives: Human papillomavirus (HPV) causes cancers at several anatomic sites, including the cervix, anus, oropharynx, penis, vulva, and vagina. In South Africa, where the prevalence of HIV is one of the highest globally, the burden of HPV-related cancers is prominent.

Methods: Using data from the South African National Cancer Registry, we described and characterized the age-standardized incidence rates and trends of HPV-associated cancers in South Africa from 2011 to 2021.

Results: In South Africa, cervical carcinoma incidence (30.4 per 100,000 person-years) during 2011 to 2021 was much higher than other HPV-related cancers. Black women had significantly higher cervical carcinoma, vulvar squamous cell carcinoma, and vaginal squamous cell carcinoma incidence compared with White women; similarly, Black men had significantly higher penile squamous cell carcinoma compared with White men. Some HPV-related cancers (vulvar, anal, and penile) significantly increased over time. Increases in vulvar squamous cell carcinoma were driven by younger ages (15-54 years), which were likely HPV-associated. Men had significantly higher oropharyngeal squamous cell carcinoma incidence compared with women, particularly for ages 75-79 years. Young women aged 15-44 years had significantly higher anal squamous cell carcinoma incidence compared with young men.

Conclusions: In a high HIV-setting, we demonstrate high HPV-cancer incidence and differences in incidence by race and sex. We also report large increases in vulvar, anal, and penile cancers in South Africa.

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DEVELOPMENT OF CIN2 AND CANCER

10 - HPV screening

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Background/Objectives: Cervical cancer rates in women living with HIV (WLHIV) in high income countries (HIC) remains 3-4 times compared to the general population, albeit much lower than the low income countries (LIC). These discrepancies between HIC and LIC are thought to be due to better HIV control and aggressive cervical cancer screening and treatment. Age standardized incident rates attributable to HIV is <5 per 100,000 compared to >20 per 100,000 in many parts of Africa.

Methods: Data from the US show an overall incident ratios of 3.8 compared to general population with the highest incidence in 20-44 and 35-39 years with no cases below 25 years. Several studies have also documented the high rate of recurrence of CIN 2,3 and cervical cancer among women WLHIV leading to several strategies to reduce recurrence with mixed results. Current screening for women living with HIV under the age recommend starting at 21 years of age at 1 year intervals until 3 consecutive normal results then at 3 year intervals. At age 30 year, similar recommendations are made if choosing cytology. In addition, co-testing is recommended at also 3 year intervals. If cytology normal/hrHPV co-testing positive, co-testing is repeated in 1 year and either abnormal, referral to colposcopy. If HPV genotyping is available, HPV 16/18+ is referred to colposcopy. if cytology is normal and HPV 16/18 is negative, repeat co-testing in 1 year.

Results: Primary HPV testing is currently not recommended in the US for WLHIV. First line treatment is recommended according to the ASCCP management guidelines for the general populations.

Conclusions: Alternative strategies for recurrent disease will be discussed including role of hysterectomy and adjuvant therapies. Unfortunately, studies in WLHIV who receive the HPV vaccine at time of treatment have been disappointing with no decrease in recurrences as seen in the general population.

HN06 - HPV and Head & Neck Forum - Submitted papers II

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#7638

Exosomal miRNA as possible liquid biomarker for HPV+ Head and Neck Squamous Cell Carcinoma

15 - Molecular markers

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Background/Objectives: Head and neck squamous cell carcinomas (HNSCC) tend to develop early lymphogenic metastasis, but reliable laboratory markers are lacking. The determination of exosomal miRNA (miR) as part of a liquid biopsy could be a new promising marker for prognosis and treatment choice of HPV+ HNSCC [1].

Methods: In the period from June 2021 to August 2022, 66 patients (50 HNSCC/16 cancer free) were acquired at the ENT clinic at UKM. A blood sample was taken from the tumor population as part of the panendoscopy and 12 months after the initial diagnosis. The exosomal miRNA load for miR-21, miR-1246, miR-let7a, miR-181a, and miR-26a was determined using rt-PCR. The expression ratios of the six miRNAs in reference to the tumor-free normal population were examined using mixed linear models for relationships with clinical parameters (UICC, smoking and alcohol behavior, HPV status) and type of therapy.

Results: Exosomal miR-21 and miR-let7a were on average three times higher expressed in HPV/p16+ HNSCC at initial diagnosis than in HPV/p16- HNSCC (p=<0.001; p=0.003). In comparison, exosomal miR-181a was increased by an average of 2.4-fold (p=0.008). After 12 months, HPV/p16+ HNSCC showed half the reduced expression of exosomal miR-21 than in HPV/p16- patients (p=0.028). 22 patients (11 HPV+ and p16+/11 HPV-) suffered of an oropharyngeal carcinoma. In this subgroup the exosomal expression of tumorsuppressive miR-let-7a was on average more than threefold higher (p=0.039) and that of miR-26a was more than fivefold higher (p=0.041) in patients without lymph node involvement (n = 11). than in patients with N1 or N2 stages (n = 11).

Conclusions: Exosomal miR-21, miR-let7a and miR-181a are significantly upregulated in HPV+ HNSCC compared to HPV- HNSCC at initial diagnosis in our study, so that these specific exosomal miRNAs can be attributed a possible association as HPV+ HNSCC liquid biomarkers. Furthermore in the oropharyngeal subgroup mir-let-7-a and miR-26a showed significant expression difference at initial diagnosis so that these specific exosomal miRNAs could be a marker for the extent of lymph node involvement in oropharyngeal cancer in context of staging and treatment choice.

References: 1. Xiao C, Song F, Zheng YL, Lv J, Wang QF, Xu N. Exosomes in Head and Neck Squamous Cell Carcinoma. Front Oncol 2019; 9: 894 [https://doi.org/10.3389/fonc.2019.00894][PMID: 31620359]

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#6799

Extensive viral studies of HPV16-associated oropharyngeal tumors.

15 - Molecular markers

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Background/Objectives: Human Papillomavirus (HPV) is an oncogenic virus responsible for many human cancers including oropharyngeal cancer. Two oncogenic proteins, E6 and E7, are responsible for HPV-induced oncogenesis, modulating the cell cycle of its host cell. The viral protein E2 is crucial to prevent cell transformation and immortalization induced by these viral oncoproteins E6 and E7. This protein can bind to its E2 Binding Sites (E2BS) to repress the expression of the oncogenes E6 and E7. However, in case of persistent infection with a high-risk HPV (HR-HPV) and the establishment of HPV-induced cancer, it is generally accepted that the viral genome integrates into the human genome. This integration leads to the loss of a part of the viral genome, including the deletion of the E2 gene, and, consequently, the loss of the repressive E2 functions on oncogenic E6 and E7 proteins expression. Surprisingly, a previous study showed that 70% of 56 HPV16-induced oropharyngeal tumors presented a pure episomal molecular status. Such findings run counter to systematic integration dogma in HPV-induced cancers. As a result, the first objective was to confirm these initial results on a larger cohort of 147 HPV16-induced oropharyngeal tumors. The second objective was to identify other oncogenic mechanisms related to HPV but not induced by its integration. Epigenetic modifications, such as methylation of CpG dinucleotides within E2BS3 and E2BS4 binding sites, had already been described as a potential mechanism explaining HPV16-induced tumorigenesis, in presence of E2 regulatory protein.[1] Thus, the second objective was to explore the level of methylation within E2BS3 and E2BS4 binding sites in 2 cohorts of HPV16-induced oropharyngeal tumors with predetermined molecular status.

Methods: The HPV16 molecular status was determined using HPV capture coupled with NGS sequencing. This approach is based on specific capture of HPV viral sequences, using 22,000 probes targeting the complete sequence of over 200 different HPV genotypes and variants, then high-throughput sequencing to obtain the entire viral genome sequence, the viral molecular status, and the insertion sites of the virus into the human genome in case of integrated virus. [2] The CpG islands methylation detection within the E2BS3 and E2BS4 regions was performed using digital droplet PCR (ddPCR). This technique offers absolute and highly precise quantification of targeted nucleic acid sequences. [3]

Results: Firstly, investigation by HPV capture coupled with NGS sequencing confirmed previous data, with 94% (n=76/81) of our HPV16-induced oropharyngeal tumors exhibiting an episomal molecular signature. Detection and quantification of E2BS3 and 4 CpG islands showed that 27% (n=20/74) of HPV16-induced tumor samples with an episomal signatures were methylation-positive. Finally, among tumor samples with an integrated or mixed viral signature, with conserved E2 gene and unmethylated (n=8/74), the investigation of genes potentially impacted by viral integration revealed 4 relevant genes to explore for potential understanding of HPV-induced oncogenic mechanisms.

Conclusions: Other mechanisms still need to be explored to explain the carcinogenic process in the remaining tumors. Understanding the oncogenic mechanisms of HPV-induced oropharyngeal cancers will not only provide new scientific knowledge but could also help identify new biomarkers to improve clinical management of these patients.

References: [1] M. Reuschenbach et al., « Methylation status of HPV16 E2-binding sites classifies subtypes of HPV-associated oropharyngeal cancers: Methylation of HPV16 E2-Binding Sites », Cancer, vol. 121, no 12, p. 1966-1976, juin 2015, doi: 10.1002/cncr.29315. [2] A. Holmes et al., « Mechanistic signatures of HPV insertions in cervical carcinomas », npj Genomic Med, vol. 1, no 1, p. 16004, mars 2016, doi: 10.1038/npjgenmed.2016.4. [3]C. M. Hindson et al., « Absolute quantification by droplet digital PCR versus analog real-time PCR », Nat Methods, vol. 10, no 10, p. 1003-1005, oct. 2013, doi: 10.1038/nmeth.2633.

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HPV-positive oropharyngeal squamous cell carcinoma-Monitoring and early response evaluation using HPV-DNA in plasma (MER-HPV)

09 - HPV testing

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Background/Objectives: HPV is the primary cause of an increase in the incidence of oropharyngeal squamous carcinomas (OPSCC) i.e. tonsil and tongue base cancer. There is raised interest for detection of HPV-DNA in plasma which could be a valuable biomarker to identify "true' residual disease or recurrence after treatment. The overall aim was to investigate the usefulness of HPV-DNA quantification in plasma among patients with OPSCC.

Methods: Patients. ForHPV-DNA assays in plasma, 150 patients with HPV-positive OPSCC and planned for curative treatment will be invited to participate. Inclusion time is expected to two years. Primary tumor. From formaline-fixed paraffin-embedded (FFPE) tumour sections DNA will be extracted (Maxwell, Promega). HPV detection and typing is performed by AllplexHPV28 (Seegene). Among HPV-positive tumors by AllplexHPV28 semi-quantitative HPV-DNA load (HPV Ct-value vs Human betaglobin Ct-value) is obtained as ratios. Plasma. From each patient, a baseline sample will be collected followed by samples once a week during seven weeks of radiotherapy treatment, as well as one month after treatment and every third month for two years. Briefly, a blood sample 8.5mL, is collected in vacutainer tube (BD ACD-A tube) and plasma obtained after centrifugation at 1700 xRPM for 7 min. DNA is extracted automatically by a Magna96-robot using the Large Volume kit (Roche) (1 mL input 50 uL output). HPV type-specific ddPCR (Biorad), with primers and probes specific for the HPV type demonstrated in the tumor is performed, and mean HPV copies/mL plasma obtained from duplicate tests. The ddPCR limit of detection was for HPV16 and HPV18 10 copies/mL (using HPV-plasmids). The corresponding copies/mL were for HPV33: 39, HPV35: 52, HPV58: 32, HPV59: 37. An "extraction"-HPV16 DNA-control (2 copies/uL) was included in each extraction-batch of samples and has hitherto been HPV-positive in each run of ddPCR.

Results: So far, 33 patients have been enrolled and in primary tumors HPV16 was most common, detected in 79% (26/33), followed by HPV33 (10%, 3/33) and single tumors with one of each HPV type 18, 35, 58 and 59. HPV-DNA was detected in 70% (23/33) of the plasma samples at baseline, with a median of 330 copies/mL (range 39-437300). Among patients with serial plasma samples HPV-DNA was detected in 85% (17/20) in at least one plasma sample during treatment. It was also observed that 50% (10/20) showed increased HPV-DNA levels after initiating radiotherapy treatment, before the levels subsided during treatment. Rapid response to treatment, defined as no HPV-DNA after 3 weeks of treatment, was found in 40% (8/20). No patients (N=20) demonstrated HPV-DNA in plasma after treatment.

Conclusions: Patients with HPV-DNA in plasma (N=23), as compared with patients without HPV-DNA in plasma (N=10), had a tendency for increased HPV-DNA ratios in tumors (mean ratio 60.5 vs 11.7, P=0.08 unpaired t-test). Conclusion Among the limited numbers of analysed patients with HPV-positive OPSCC, the ddPCR had a sensitivity of 70% for detection of HPV-DNA in baseline plasma samples. The plasma HPV-DNA positive patients showed a tendency for increased HPV-DNA levels in tumours. Patients with rapid HPV-DNA clearance during treatment might be of interest for future studies of deintensified therapy. Additional results will be presented at the conference.

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#7004

NF-κB signaling pathway activity leads to identification of novel molecular biomarkers in HPV-associated head and neck cancer

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The human papillomavirus (HPV) is a causative agent in a proportion of head and neck squamous cell carcinoma (HNSCC) displaying a significantly favorable prognosis and overall better survival as compared to HPV negative HNSCC. Incidence of HPV related HNSCC is on the rise due to an increase in the incidence of HPV infection. Treatment includes chemotherapy along with intense radiotherapy leading to severe side-effects like difficulty swallowing, changes to voice, hair loss and lymphoedema among others. Precision medicine would revolutionize the treatment of head and neck cancer by accurately identifying patients that are at low risk of recurrence, reduce treatment related side-effects and aid in overall improvement in quality of life of patients after treatment. This generates the need to develop biomarkers to identify patients with less aggressive tumors as candidates for treatment de-escalation.

Methods: We applied an unbiased approach (weighted gene correlation network analysis (WGCNA)) that allows detection of autocorrelated gene sets on 3 independent cohorts of HPV+ HNSCC and created 22 consensus transcriptional modules by selecting genes that grouped together in WGCNA analyses from all 3 cohorts.

Results: Interestingly, only 1 module intrinsically divided HPV+ HNSCC into 2 subtypes, displaying different mutational profiles, mutational signatures, HPV gene expression patterns, HPV integration status, and patient survival. Gene set enrichment analysis revealed that this module was enriched in NF-kB genes and strongly associated with NF-κB signaling, confirming our prior findings that defined HPV+ HNSCC subtypes by presence or absence of NF-kB regulators, TRAF3 or CYLD defects and by the NF-κB activity classifier. We hypothesized that NF-kB-driven intrinsic tumor characteristics contribute to increased sensitivity of NF-kB active HPV+ head and neck tumors to radiation, providing patients survival benefits. Indeed, TRAF3 or CYLD deletion dramatically increased radiation sensitivity of HPV+ head and neck cancer cells. As we began to investigate mechanisms of radiation sensitization associated with TRAF3 and CYLD deletion, we found that activation of NF-κB significantly correlated with marked downregulation of nuclear factor erythroid 2-related factor 2 (NRF2) activity in tumors from 3 independent cohorts, as well as in HPV+ HNSCC cells that harbor constitutively active NF-kB due to deletion of TRAF3 or CYLD. Interestingly, TRAF3 CRISPR KO cells had lower NRF2 protein levels that were restored by MG132 treatment, indicating an involvement of KEAP1/CUL3 mediated proteasomal degradation of NRF2.

Conclusions: In summary, our data showcases an inverse correlation between NF-kB and NRF2 pathways in HPV+ HNSCC. Currently, there are no prognostic biomarkers to distinguish patients who require aggressive therapy versus those that are appropriate for reduced intensity treatment. Risk stratifying subtypes of HPV+ HNSCC will serve as the foundation for new or de-intensified therapies, as well as for evidence guided personalize treatment to maximize cancer treatment impact while minimizing treatment related morbidity for patients.

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#6680

HPV viral load is higher in HPVDNA/p16+ OPSCC as compared to that in HPVDNA+/p16- OPSCC but does not differ significantly between OPSCC Subsites.

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Patients with human papillomavirus DNA positive (HPVDNA+) and p16ink4a overexpressing (p16+) oropharyngeal squamous cell carcinoma (OPSCC), especially those with cancer in the tonsillar and base of tongue subsites as compared to other OPSCC subsites have a better clinical outcome than those with corresponding only HPVDNA+ or only p16+ cancer. Likewise having a high viral load has been suggested to be a positive prognostic factor. We therefore hypothesized, that HPV load could vary depending on OPSCC subsite, as well as with regard to whether the cancer was HPVDNA+ and p16+, or only HPVDNA+, or only p16+ and that this affected outcome.

Methods: To address these issues HPV viral load was determined by digital droplet HPV PCR in tumor biopsies of 270 OPSCC patients of which 235 had HPVDNA+/p16+, 10 had HPVDNA+/p16- and 13 had HPVDNA-/p16+ cancer and also tested in 12 HPVDNA-/p16- tumors. The latter two groups as HPV DNA negative controls.

Results: We found no statistically significant differences in viral load between OPSCC subsites, however HPVDNA+/p16+ cancers had a significantly higher viral load than those with HPVDNA+/p16- cancers. When viral load was assessed for correlation to clinical outcome, patients having a lower viral load in their tumors generally tended to have a better clinical outcome than those with a higher viral load, however, the difference was not statistically significant.

Conclusions: To summarize, HPVDNA+/p16+ OPSCC samples had a higher viral load than those that were HPVDNA+/p16-, but we could not disclose that HPV viral load differed significantly between different OPSCC subsites or that a low or high viral load correlated in a statistically significant way to clinical outcome.

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#6912

COMPREHENSIVE MRNA EXPRESSION PROFILING FOR HPV ONCOGENES, P16 AND CELLULAR BIOMARKERS FOR DETERMINATION OF HNSCC HPV ETIOLOGY

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Head and neck squamous cell carcinoma (HNSCC) driven by Human Papillomaviruses (HPV) have a better prognosis compared with HPV-negative HNSCC. Patients bearing HPV-driven HNSCC may receive de-escalated chemo-radiation. Immunohistochemistry (IHC) for p16 is used as surrogate for high-risk (hr) HPV, however, we found in a subset of HPV-negative HNSCC p16 positive, and inversely lack of p16 expression in HPV DNA positive tumors. Such patients have a worse outcome and may be misclassified by p16 IHC detection only. Quantitative comprehensive testing for active expression (mRNA) strength is needed. We developed a multiplexed mRNA quantifying assay QuantiGene-Molecular-Profiling-Histology (QG-MPH) reporting expression levels of HPVE7 and cellular biomarkers including p16. The current study aimed to compare QG-MPH, HPV DNA PCR and p16 IHC for characterization of HNSCC etiology.

Methods: Ninety-seven FFPE blocks from primary HNSCC of untreated patients were evaluated by Multiplexed Genotyping (MPG) for HPV L1 DNA and by IHC for p16. QG-MPH assay quantified HPV E7, p16 as well as proliferation and tumor marker mRNA expression (reported as rMFI).

Results: HrHPV L1 DNA tested positive in 48 (49.5%) of 97 cases, while 46 (47.4%) cases tested HPV negative and three (3.1%) invalid. 26 (54.2%) HPV DNA positive cases had hrHPV E7 mRNA detected above cutoff. Four (8.7%) out of 46 hrHPV L1 DNA negative cases tested hrHPV E7 mRNA positive. Three MPG invalid cases were valid for QG-MPH with one HPV E7 mRNA positive and two negative. HrHPV E7 mRNA tested positive in 31 (32%) of 97 cases while 60 (61.9%) were negative and six (6.1%) invalid. Among these 60 E7 mRNA negative cases, 21 (35%) were hrHPV L1 DNA positive, 37 (61.7%) negative and two (3.3%) invalid. Expression of p16 mRNA was correlated to HPV status based on L1 DNA and E7 mRNA detection. The highest expression of p16 (median rMFI 138.8, range 62.6-330.1) was present in the hrHPV L1 DNA+/E7 mRNA + group. The lowest p16 mRNA expression (median rMFI 7.1, range 0-125.1) was in the hrHPV L1 DNA+/E7 mRNA- group (pinf0.001). The HPV L1 DNA-/E7 mRNA+ group should probably be classified as hrHPV+ with low L1 DNA copy number but high E7 mRNA transcription rate. Taken together the median rMFI of p16 mRNA in the E7 mRNA+ group was 129.8 (range 8.9-330.1) and in the hrHPV L1 DNA-/E7 RNA- group 16.8 (range 0-327.2). The corresponding p16 IHC will be shown at the conference.

Conclusions: HPV L1 DNA and E7 mRNA detection was discrepant in nine (9.3%) of 97 HNSCC cases. In the HPV L1 DNA+/E7 mRNA- group hrHPV maybe an innocent bystander in non-HPV driven HNSCC. The HPV L1 DNA-/E7 mRNA- group are truly HPV negative HNSCC. p16 mRNA was statistically significantly higher expressed in the hrHPV L1 DNA+/E7 mRNA+ group when compared with the HPV L1 DNA+/E7 mRNA- and HPV L1 DNA-/E7 mRNA- groups. Strong expression even above the median of L1 DNA+/E7 mRNA+ cases of p16 mRNA was observed in four (14.3%) of hrHPV L1 DNA-/E7 mRNA- cases. p16 alone may not be a reliable marker leading to misclassification of HNSCC cases and therapeutic planning. Comprehensive expression quantification by QG-MPH may support more precise classification of HPV etiology. Limitations were use of long-term archived FFPE blocks that may have contained degraded DNA and mRNA, adversely affecting the sensitivity of the detection. Further studies with more recent FFPE material or with fresh/frozen tissues are warranted.

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#7040

LINE-1 METHYLATION IN HPV16-POSITIVE OROPHARYNGEAL CANCER: A POTENTIAL PROGNOSTIC MARKER OF POOR PROGNOSIS

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Retrospective studies showed that hypomethylation of LINE-1, a surrogate of global DNA methylation, is a negative prognostic factor in oropharyngeal squamous cell carcinoma (OPSCC), independently from clinical factors and HPV status. Interestingly, HPV-positive patients with LINE-1 methylation <55% showed an almost 5-fold higher risk of death than hypermethylated ones, with an overall survival as poor as HPV-negative patients [PMID: 28572862].

Methods: Since 2019, an ongoing prospective study has been enrolling patients with OPSCC in nine cancer centers in Northern Italy, collecting tumor tissue, blood samples, and comprehensive clinical data. HPV16 E6 DNA was quantified on tumor tissue using real-time quantitative PCR (qPCR). LINE-1 methylation was evaluated on tumor tissue samples by methylation-specific qPCR.

Results: Up to date, 134 OPSCC patients have been enrolled, including cancer of the tonsil (n=74; 55.2%), base of tongue (n=47; 35.1%), and other subsites (n=13; 9.7%); additional 18 patients with cancer of unknow primary (CUP) were excluded from the present analysis. HPV16 DNA was found in 54.3% of cases, with significant variability across cancer subsites: 65.7% in base of tongue, 57.1% in tonsil, and 16.7% in other subsites (p<0.001). LINE-1 methylation was higher in HPV16-positive patients (median: 55.8%, interquartile rage [IQR]: 42.5-68.5) than HPV16-negative ones (median: 40.7; IQR: 23.9-59.1; p=0.003). Differently from HPV16-negative patients, among HPV16-positive ones, LINE-1 methylation was similar across strata by subsites, smoking status, and T stage. Data from the present investigation are presently not mature to purse the study aims (median follow-up: 12.3 months). Nonetheless, preliminary results confirm the findings previously reported [PMID: 28572862]: indeed, the median LINE-1 methylation was lower (50.7%) among HPV-16 positive OPSCC patients who relapsed than those who did not (56.0%).

Conclusions: The preliminary results from this ongoing, prospective study confirm the prognostic value of LINE-1 methylation <55% in HPV16-positive patients with OPSCC. Notably, among these patients, LINE-1 methylation status is not associated to recognized prognostic factors, namely tobacco smoking, and T stage [PMID: 20530316]. This confirms the potential of LINE-1 methylation to identify HPV16-positive patients with poor prognosis. Furthermore, data collected herein will allow to better characterize this subgroup of patients from a molecular point of view.

References: Furlan C, Polesel J, Barzan L, Franchin G, Sulfaro S, Romeo S, Colizzi F, Rizzo A, Baggio V, Giacomarra V, Dei Tos AP, Boscolo-Rizzo P, Vaccher E, Dolcetti R, Sigalotti L, Fratta E. Prognostic significance of LINE-1 hypomethylation in oropharyngeal squamous cell carcinoma. Clin Epigenetics. 2017 May 30;9:58. doi: 10.1186/s13148-017-0357-z. PMID: 28572862; PMCID: PMC5450111. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul 1;363(1):24-35. doi: 10.1056/NEJMoa0912217. Epub 2010 Jun 7. PMID: 20530316; PMCID: PMC2943767.

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#7861

Tumour inflammation signature and expression of S100A12 and HLA class I improve survival in HPV-negative hypopharyngeal cancer

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Hypopharyngeal squamous cell carcinoma (HPSCC) has a very poor prognosis. Local surgery may increase survival, but is often avoided due to significant post-op co-morbidities. Since prognostic markers are lacking, the aim was to find predictive biomarkers that identify patients whose response to oncological treatment is poor and who may benefit from primary surgery to increase survival.

Methods: Pretreatment biopsies from 23 HPSCC patients, 3 human papillomavirus (HPV) positive and 20 HPV-negative, were analyzed for expression of 750 mRNAs using the Nanostring nCounter IO360 panel in relation to 3-year survival. Validation was performed through immunohistochemistry (IHC) for HLA class I and S100A12 in 74 HPV-negative HPSCC samples.

Results: Clustering identified a subset of HPV-negative HPSCC with favorable prognosis and a gene expression signature overexpressing calgranulins and immune genes, distinct from that of HPV-positive HPSCC. Enrichment analysis showed immune signaling, including the tumor inflammation signature, to be enriched in surviving patients. IHC validation confirmed high S100A12 and HLA class I expression to correlate with survival in HPV-negative HPSCC. This shows that immune activity is strongly related to survival in HPV-negative HPSCC.

Conclusions: Enrichment of the tumor inflammation signature indicates a potential benefit of immunotherapy. Low expression of both HLA class I and S100A12 could be used to select patients for local surgery.

References: 10.1038/s41598-020-80226-z

SS27 - RISCC: Implementation of risk-based cervical cancer screening in Europe

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#7737

Model-based evaluation of risk-based screening - WP5

39 - Public health

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Background/Objectives: Screening for cervical cancer is a globally recommended public health policy. Many risk factors are known, but so far "one-size-fits-all" screening programs have been mostly implemented, providing suboptimal protection for women at high risk, suboptimal allocation of resources and substantial screening-related harms. Development of risk-stratified screening is a priority because cervical cancer is on the rise in many countries, the uptake of screening remains moderate in subpopulations at high risk, and costs related to screening are high. The overarching objective of the EU-funded RISCC consortium (RISK-BASED SCREENING FOR CERVICAL CANCER) is to develop effective and cost-effective risk-based screening algorithms based on age of the woman, screening history, HPV vaccination status, and population vaccination coverage.

Methods: The predictive assessment of effectiveness, screening-related harms, and cost- effectiveness of risk-based screening algorithms will be performed using a set of mathematical models of transmission of multiple oncogenic HPV types and disease progression from infection to cervical cancer. Risk profiles based on screening history are being developed using joint data from several large European randomized HPV screening trials with long-term follow-up, HPV self- sampling trials, and registries of both cytology- and HPV-based screening programs. Risk profiles based on vaccination status are being developed for cohorts with varying screening and vaccination coverage using data from a community randomized vaccination trial, linked vaccination/screening/cancer registries, and a cohort of women vaccinated at screening age. Since the implementation of cervical cancer screening policies is highly heterogeneous across European countries, we have defined a limited number of risk-stratified policies flexible enough to be adapted to virtually any setting in Europe and we are currently assessing the effectiveness and cost-effectiveness of such policies across the continent. To do that we have developed and tested an analytical framework to obtain estimates either using country-specific data, whenever available, or approximating such data by clustering countries according to epidemiological similarities.

Results: Our systematic assessment of available data has allowed us to inform RISCC's mathematical models with a) behavioral and epidemiological data and b) information about ongoing HPV vaccination and cervical cancer screening policies from European countries. Currently, we are adapting our models to each EU country, and we expect to have a complete assessment of effectiveness and cost-effectiveness of a range of risk-based screening policies by the end of year 2024.

Conclusions: This is the first attempt to design risk-stratified screening algorithms adaptable to any European country and to assess their impact and cost-effectiveness. The proposed approach accounts for the existing heterogeneity in the implementation of cervical cancer screening across the continent. The findings, methodology, and tolls of this project will provide a substantial contribution to elimination of cervical cancer in Europe.

SS25 - Debate session

Baussano Iacopo
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#7736

What is the best strategy for HPV immunization surveillance: Cross-sectional with population-level data VS. record linkage with subject-level data.

39 - Public health

Baussano I[1]

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Background/Objectives: Ensuring that HPV vaccination programs have an actual population-level impact on the cervical cancer burden is key to maintaining political commitment, ensuring adequate resources, and optimizing the allocation of resources dedicated to cervical cancer control. Since the ultimate goal of introducing HPV vaccination is cervical cancer incidence reduction, the most direct evidence of effectiveness, in principle, could be obtained through population-based cancer registries. However, in practice, in most resource-limited settings this is not currently feasible, because PBCR are resource-demanding to establish and maintain and, in some settings, can be affected by under-reporting and under-detection. Furthermore, the impact of HPV vaccination on cervical cancer at a population-level takes decades to be observed, due to the long latency between HPV infection and cervical cancer occurrence. In contrast, the effectiveness of vaccination against cervical cancer can be seen early and indirectly assessed by monitoring age- and type-specific prevalence of carcinogenic HPV infections through cross-sectional population-based surveys among unvaccinated and vaccinated birth-cohorts. The objective of this presentation is to illustrate and discuss the advantages and limitations of using series cross-sectional with population-level surveys to assess the population-level effectiveness of HPV vaccination.

Methods: The International Agency for Research on Cancer (IARC) has a very long experience of monitoring age- and type-specific prevalence of carcinogenic HPV infections through cross-sectional population-based surveys to assess both HPV burden and the effectiveness of HPV vaccination. Building on that experience, IARC is setting up International Coordination Center (ICC) to develop standardized and exportable procedures to plan, prepare, conduct, monitor, and analyze findings from HPV prevalence cross-sectional surveys targeted at women from selected populations in resource-limited settings.

Results: This initiative, named "Chronos', has been launched in late 2023 and will take a few years to be consolidated. The aim is to transfer to local personnel from partner institutions in selected countries the necessary skills and tools to perform the different phases of the cross-sectional surveys through a standardized training. The corresponding fieldwork, i.e., HPV prevalence survey implementation, will then be monitored by the ICC to ensure adequate quality standards, and finally the collection of acquired data will be centralized to allow for comprehensive, transparent, and standardized data analyses. These surveys will be designed to monitor the effectiveness, i.e., population-level impact, of HPV vaccination.

Conclusions: Data obtained from cross-sectional surveys serve both descriptive and predictive purposes. Empirical estimates of HPV vaccination effectiveness inform local public health authorities of the overall burden of HPV in the population and on possible relevant differences in risk across that same population. Such estimates can also be used to predict, through advanced quantitative modelling, the expected long-term health impact of HPV vaccination (and cervical cancer screening) on the cervical cancer burden. Finally, if cost information is available on the vaccination program and cervical cancer management, it is also possible to estimate the expected economic impact of introducing HPV vaccination in a specific population.

SS28 - Cervical cancer screening in LMICs

Chinula Lameck
Malawi
Chinula Lameck
Malawi

#7621

SINGLE VISIT SCREEN-AND-TREAT STRATEGY WITH XPERT-BASED HPV SELF-TESTING AND THERMAL ABLATION TREATMENT FOR WOMEN IN LILONGWE, MALAWI

10 - HPV screening

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Background/Objectives: The World Health Organization now recommends Human Papillomavirus (HPV)-based primary screening for cervical cancer prevention, including for women living with HIV (WLWH). Visual inspection with acetic acid (VIA) is widely used for screening in resource-limited settings as it is inexpensive and allows for same-day screen-and-treat strategies (i.e., single visit approaches). Gene Xpert platform allows for 1-2 hours HPV results. However, same-day HPV-based screen-and-treat strategies have not been extensively evaluated. Therefore, we evaluated the same-day completion of a GeneXpert-based HPV self-testing screen-triage-treat algorithm for cervical cancer prevention among WLWH and women without HIV.

Methods: We conducted a prospective study of an HPV-based screen-triage-treat strategy in Lilongwe, Malawi. We enrolled women aged 25-50 years with no history of cervical, vaginal, or vulvar dysplasia or cancer, and no prior hysterectomy. We excluded pregnant women and those less than 12 weeks post-delivery. The screen-triage-treat strategy consisted of: (1) GeneXpert HPV testing of self-collected samples, (2) VIA and colposcopy for HPV-positive women, and (3) thermal ablation for HPV-positive/ablation-eligible women. We collected cervical biopsies if colposcopy was abnormal or cervical cytology if colposcopy was normal, and endocervical curettage (ECC) on all HPV+ women, to validate the HPV results and VIA/colposcopy findings against the endpoint of high-grade cervical intraepithelial neoplasia (CIN2/3) or cancer. Same-day completion rate was evaluated as a proportion of HPV+ women on self-collected sample who underwent VIA/colposcopy triage for thermal ablation. At 24 weeks post-treatment, women who received thermal ablation and had CIN2/3 at baseline were follow-ed up for provider-collected cervical sample for HPV testing, colposcopy-directed biopsy, or cervical cytology and ECC.

Results: Between June 2020 and February 2022, we enrolled 1250 women, 625 of whom were WLWH and 625 were women without HIV. The median age was 35 years (IQR 30-40), 870 (69.6%) were married or living with their male partner, 1178 (94.2%) had no history of smoking, and 698 (55.8%) had no prior cervical cancer screening. Of 625 WLWH, 588 (99.7%) were on antiretroviral therapy (ART), of which 566 (96.3%) were on ART for at least 6 months. Among 1250 women, 476 (38.1%) were HPV+, 53 (11.1%) had CIN2/3, and 2 (0.4%) had invasive cervical cancer. Of 476 HPV+ women, 454 (97.0%) underwent VIA and colposcopy on same day of HPV self-testing. The overall completion rate of same day screen-triage-treat algorithm was 0.97 (95% CI: 0.95 - 0.98), with 0.96 (95% CI 0.93-0.98) among WLWH and 0.98 (95% CI: 0.95-0.99) among women without HIV. Of 454 women who had VIA/colposcopy on same day of HPV self-testing, 126 (28%) had abnormal findings, of whom 106 (84%) were eligible for thermal ablation. All eligible women received ablation on the same day.

Conclusions: In this large study in Lilongwe, Malawi, there was high rate of same-day completion of screen-triage-treat strategy with Gene Xpert HPV self-testing, VIA/colposcopy triage, and thermal ablation treatment. Gene Xpert testing and HPV self-sampling offer a promising platform for a single-visit approach to cervical cancer screening in sub-Saharan Africa and similar settings. Other HPV point-of-care platforms with even faster turnaround testing times may make our study findings more generalizable to non-study settings.

References: 1.WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. 2. Bruni L, Serrano B, Roura E, Alemany L, Cowan M, Herrero R, Poljak M, Murillo R, Broutet N, Riley LM, de Sanjose S. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. Lancet Glob Health. 2022 Aug;10(8):e1115-e1127. doi: 10.1016/S2214-109X(22)00241-8. Erratum in: Lancet Glob Health. 2023 Jul;11(7):e1011. PMID: 35839811; PMCID: PMC9296658.

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#7765

CROWDSOURCING HPV SCREENING AND VACCINATION STRATEGIES FOR MOTHERS AND DAUGHTERS IN NIGERIA: FINDINGS FROM A COMMUNITY-LED PARTICIPATORY EVENT

10 - HPV screening

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Background/Objectives: Evidence-based HPV prevention interventions exist but are sub-optimally implemented in African countries like Nigeria.1-3 To enhance HPV vaccination and cervical cancer screening in Nigeria, we organized a designathon that engaged mother-daughter teams to develop community-driven strategies. We used the PEN-3 cultural model's relationship and expectation domain to identify empowerment-based perceptions, enablers, and nurturers to leverage in implementing these strategies. We emphasize participatory action research methods like crowdsourcing through designathons and innovation bootcamps in co-creating solutions and raising awareness for HPV and cervical cancer in Nigeria.

Methods: We organized a three-phase designathon for women (30-65 years) and girls (11-26 years) in Nigeria. First, we launched a 10-week national crowdsourcing open call for ideas on community-driven strategies to support HPV screening among women and vaccination among girls. The open call was promoted widely on social media and at in-person gatherings. Second, judges graded all eligible entries based on relevance, feasibility, innovation, potential impact, and mother-daughter team dynamics. The top 16 teams (4 to 6 members each) were invited to a 3-day, in-person event in Lagos to refine and pitch their ideas to a panel of expert judges. Third, a 4-week innovation bootcamp followed, attended by the top 8 teams, which provided teams with training and informational support through peer mentoring and education. We present descriptive data on participants and themes from textual submissions, key informant interviews, and evaluations.

Results: Entries (n=612) were received online (n=392), in-person (n=99), via the WhatsApp instant messaging application (n=92), and emails (n=31) from 27 Nigerian states. The average age of participants for daughters was 19 years and 39 years for mothers. Themes from the top 16 strategies included leveraging local leaders (5/16), faith-based networks (4/16), educational systems (4/16), annual female-related celebrations (2/16), and other community networks such as mobile, media, and telehealth channels (7/16) to promote awareness of cervical cancer prevention services. Using the PEN-3 perception construct, bootcamp attendees reported increased knowledge (96%) of HPV and cervical cancer in Nigeria and of gender roles (92%) as an asset in healthcare delivery in Nigeria. Participants also identified religious and local leaders as enablers, in addition to the cost of HPV services and mother-daughter relationships, complemented by support from fathers and extended family as nurturers. Seven strategies from the bootcamp are being piloted in these seven Nigerian states: Ogun, Akwa-Ibom, Bayelsa, Lagos, Oyo, Cross River, and Anambra.

Conclusions: Our participatory action research approach using crowdsourcing, emphasizes local networks and resources as significantly increasing awareness and knowledge about cervical cancer in communities. There is a need for further implementation research on the impact and sustainability of these strategies.

References: 1. Anyebe E, Opaluwa S, Muktar H, Philip F. Knowledge and practice of cervical cancer screening amongst nurses in Ahmadu Bello University Teaching Hospital Zaria. Cancer 2014; 4(27): 33-40. 2. Hyacinth HI, Adekeye OA, Ibeh JN, Osoba T. Cervical cancer and pap smear awareness and utilization of pap smear test among Federal civil servants in North Central Nigeria. 2012. 3. Igwilo A, Igwilo U, Hassan F, Idanwekhai M, Igbinomwanhia O, Popoola A. The knowledge, attitude and practice of the prevention of cancer of the cervix in Okada Community. Asian Journal of Medical Sciences 2012; 4(3): 95-8.

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#7781

Pay-it-forward to increase HPV vaccine uptake compared to user-paid vaccination: A population-based randomized controlled trial in China

06 - HPV prophylactic vaccines

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Background/Objectives: Over 15% of global cervical cancer deaths occur in China, but HPV vaccination rates are low among adolescent girls. Barriers to vaccination include limited public funding and poor community awareness. Innovative approaches are needed to address these issues. Pay-it-forward offers an individual a subsidized service, and an opportunity to donate to help others access vaccinations. Our randomized control trial assessed the effectiveness of pay-it-forward in improving HPV vaccination among girls aged 15-18 years in China.

Methods: Eligible participants were randomly selected from community name lists, in Chengdu, China, and invited via telephone calls. Using the sealed envelope method, we randomly assigned them into standard-of-care and pay-it-forward arms at a 1:1 ratio. Pay-it-forward participants received a fixed community-contributed subsidy (47·7 USD) to support the HPV vaccination, and an opportunity to donate to support others. Participants in the standard-of-care (or control) arm paid for their own vaccination. Data about girls and their caregivers were collected. The primary outcome was the uptake of the first-dose HPV vaccination ascertained by clinical records. We also collected data on the number of girls who donated and/or wrote postcards. The financial cost per person vaccinated was calculated using the micro-costing method for each arm. This study was registered on the Chinese Clinical Trial Registry (ChiCTR2200055542), has concluded its recruitment phase.

Results: Between 6 July 2022 and 9 June 2023, a total of 321 participants (via caregivers) were recruited and randomized to the control arm (n=160) or the pay-it-forward arm (n=161). Most caregivers were female (80·1%), married (80·4%), and had a high school education or less (72·0%). A total of 34·2% (55/161) of girls in the pay-it-forward arm received the HPV vaccine, and 17·5% (28/160) of girls in the standard-of-care arm received the vaccine, corresponding to a proportion difference of 16·7% (95% CI: 7·2-26·0, P=0·0006). Among 55 girls in the pay-it-forward arm who received the vaccination, 39 (70·9%) of caregivers donated, and 37 (67·3%) wrote a postcard message to support future girls. The financial cost per person vaccinated was $294 in the standard-of-care group and $230 in the pay-it-forward group.

Conclusions: The pro-social pay-it-forward strategy was effective and cost-saving in increasing HPV vaccination among teenage girls.

References: 1. Qiao J, Wang Y, Li X, et al. A Lancet Commission on 70 years of women's reproductive, maternal, newborn, child, and adolescent health in China. The Lancet 2021; 397(10293): 2497-536. 2. Wallender E, Peacock G, Wharton M, Walensky RP. Uninsured and Not Immune - Closing the Vaccine-Coverage Gap for Adults. N Engl J Med 2023; 389(3): 193-5.

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#7264

FEASIBILITY OF SELF-ADMINISTERED, INTRAVAGINAL 5-FLUOROURACIL (5-FU) CREAM AS ADJUVANT THERAPY FOLLOWING CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 AND 3 (CIN2/3) TREATMENT IN HIV-POSITIVE WOMEN IN LMICS: A PILOT STUDY

38 - Low resource settings

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Background/Objectives: Women living with HIV (WLWH), the majority of whom live in Sub-Saharan Africa (SSA), are up to six times more likely to get cervical cancer and are in urgent need of effective secondary prevention. However, current cervical precancer treatment in WLWH is limited by high recurrence rates, up to 30% following thermal ablation, the most accessible precancer treatment in Kenya and SSA. Prior studies in high-income countries (HIC) have demonstrated that 5-Fluorouracil (5-FU), an antimetabolite drug that is generic and easily accessible in SSA, can be used intravaginally as adjuvant therapy in WLWH to reduce recurrence rates. While the safety, acceptability, and efficacy of self-administered 5-FU for cervical precancer treatment has been demonstrated in high-income countries, 5FU has not been studied among WLWH in SSA, who bear the greatest burden of cervical cancer.

Methods: We are conducting a pilot study investigating the feasibility of using 5-FU as an adjuvant, self-administered intravaginal therapy following cervical intraepithelial neoplasia grade 2/3 (CIN2/3) treatment among twelve WLWH in Kenya (ClinicalTrials.gov NCT05362955). All twelve participants are enrolled in this single-arm study, with 80% of follow-up visits complete. Participants self-administer 2g of 5% 5-FU intravaginally, once a night, every other week for eight applications, and are seen in the clinic on intervening weeks for safety and adherence evaluation by a study clinician. The primary objective is to determine safety, defined as the type, frequency, and severity of adverse events (AEs) using a standardized grading scale. The secondary objectives are tolerability, adherence, and acceptability.

Results: Study participants' mean age and CD4 counts are 43.9 years and 781 cells/mm3, respectively. Seven participants (58%) have completed less than a primary education, and 91.7% have a secondary education or less. On safety evaluations so far, all participants reported at least one adverse event (AE), with increased vaginal discharge (29.7%), vaginal irritation (12.2%) and vaginal dryness (10.8%) being most common. All AEs were grade 1 (mild) and lasted an average of 1-5 days. On pelvic exam, provider-observed AEs included cervical erythema (43.3%), discharge (30%), and superficial, small (less than 0.5cm) epithelial disruption (23.3%) at the introitus or on the vulvar. All provider-observed AEs were grade 1 (mild), and the epithelial disruptions/abrasions noted were self-limited and resolved with perineal care. So far, 95% adherence is supported using both self-report and validated objective measures, and all participants have tolerated all eight doses of 5FU so far.

Conclusions: To achieve the WHO 90/70/90 Cervical Cancer Elimination target by 2030, innovative and resource-appropriate strategies to improve cervical precancer treatment among WLWH. In this first-in-Kenya Phase I trial, we demonstrate excellent safety, tolerance, and adherence to self-administered intravaginal 5FU as adjuvant therapy among WLWH at high risk of CIN2/3 recurrence. Randomized efficacy trials are needed to investigate whether adjuvant 5FU can improve CIN2/3 treatment outcomes following thermal ablation or cryotherapy among WLWH in Africa.

SS31 - The utility of urine for improved cervical cancer prevention

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#7757

EVALUATION OF THE EFFICACY OF FIRST VOID URINE AND VAGINAL SELF-SAMPLING IN A FRENCH PRIMARY SCREENING COHORT OF UNDER-SCRENNED WOMEN: FIRST STUDY OUTCOMES OF THE CAPU4 STUDY.

13 - Self-sampling

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Background/Objectives: Cervical cancer (CC) is the second most common cause of death by cancer in women under the age of 45 years in developed and industrialized countries worldwide. Self-sampling may improve participation in cervical cancer secondary prevention programs by women who do not respond or respond irregularly when invited to contact a health professional for the collection of a cervical specimen. It could also help resolve access problems in areas with low physician density. In France, two administrative departments (Mayenne and Sarthe) have the lowest physician density and the lowest rates cervical screening coverage. However, despite health professionals playing a major role in CC screening, little is known about their opinions on cervical cancer screening and self-sampling in areas with low physician density. The present study examined barriers to screening, effective screening strategies, and the advantages and disadvantages of sending women urine or vaginal self-sampling kits by exploring the viewpoints of health professionals working in rural, semi-rural areas or in priority intervention areas (PIAs).

Methods: This qualitative study is part of the CapU4 randomized trial. It investigated the opinions of 59 healthcare professionals involved in screening (gynecologists, general practitioners, and midwives) through semi-structured interviews. Healthcare professionals working in rural, semi-rural areas or in the PIAs of Mayenne or Sarthe departments (Pays de la Loire, France) were selected. The interviews were analyzed using standard qualitative content analysis.

Results: Given the PIA context, our analysis revealed several barriers to screening strategies.The results show that organized screening program for CC seems insufficient, especially for underscreened women. We provided recommendations that may contribute to improving CC screening participation, such as: continue sending out invitation letters as part of the routine screening program; provide information for the public: television campaigns, articles in women's magazines; pursue face-to-face meetings with women (nursing homes, depist-bus mobile screening unit); raise general practitioners awareness of cervical screening. Also, health professionals confirmed trust in the use of vaginal self-sampling. Urine self-sampling should be an alternative solution (e.g., for women with vaginismus). The health professionals identified several limitations of the self-sampling kit (incomplete, complex instructions, poor anatomical knowledge, obesity). These limitations gave the following recommendations for future screening campaigns: include easily understandable user instructions in the sent self-sampling kits; involve healthcare professionals: raising awareness, informing, explanation and translation; continue to inform and train healthcare professionals in the use of these kits; reassure women about their ability to carry out self-sampling and about the availability of a professional if necessary; improve links to healthcare professionals (who should be consulted when the HPV test result is positive); make it clear that self-sampling does not replace gynecological consultation; make the kits free of charge.

Conclusions: Offering self-sampling to women who do not screening or underscreening may be an appropriate strategy in French areas with low physician density for meeting the World Health Organization's objective of eliminating CC. It is a strategy that healthcare professionals consider acceptable for PIAs.

SS30 - Indications for methylation testing in cervical screening and in the diagnosis of cervical and non-cervical HPV-associated lesions

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#7759

Clinical indications for methylation markers in cervical cancer screening and management of CIN.

17 - Methylation

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Background/Objectives: DNA methylation is an emerging biomarker for the management of HPV-positive women in cervical cancer screening and for risk stratification of women diagnosed with cervical intraepithelial neoplasia (CIN). Aberrant DNA methylation of human genes and HPV genome has been found associated with carcinogenesis of the uterine cervix.

Methods: Detection of methylated DNA can accurately be performed by molecular methods on different sample types, including cervical tissue, clinician-collected cervical samples, self-collected vaginal samples and urine.

Results: Over the past years, various studies on methylation markers have shown promising results as triage marker to improve HPV-based cervical cancer screening. Methylation markers represent an excellent alternative or additive to cytology and HPV genotyping, to reduce the number of unneeded colposcopy referrals and interventions of HPV-positive women. CIN2/3 lesions represent heterogeneous disease entities that harbor lower and higher risks for cancer progression. The ability to define lesions with potential short-term risk of progression to cancer by a tumor-like, or high-risk methylation pattern is gaining increased attention. Recent studies have demonstrated the value of methylation markers in management of women with CIN2/3 and post-treatment monitoring. Methylation assays could be valuable to reduce overtreatment.

Conclusions: This presentation will give an overview of clinical applications of methylation assays in cervical cancer screening and management of CIN. DNA methylation markers can help to enhance the accuracy and efficiency of cervical cancer screening programs, and can optimize management of women with CIN by improved risk stratification to prevent overtreatment of women without clinically relevant disease.

HN08 - HPV and Head & Neck Forum - Recurrent respiratory papillomatosis (RRP)

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#7652

Epidemiologic trends in RRP

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Recurrent respiratory papillomas (RRP) are a potentially devastating disease of the larynx affecting children and adults infected with HPV types 6 and 11. These HPV subtypes were covered by the original HPV-4 vaccine and are also included in the HPV-9 vaccine. With uptake of the vaccine in the developed and developing world a noticeable decline in new cases of RRP is being appreciated.

Methods: Will review the impact of vaccination against HPV on the incidence of RRP in several countries and the WHO goals for worldwide vaccination.

Results: Results from the CDC-funded JORRP study showing a 10-fold reduction in new cases of RRP will be presented along with the astonishing reductions noted on the Australian continent. Efforts to document these declines in the UK and Canada will be presented. The newly launched AORRP registry study in the US to document similar effects in adults with RRP will be outlined.

Conclusions: Through vaccination efforts, new cases of juvenille onset RRP have declined significantly in the developed world. Effects on adult-onset disease are still to be determined. Efforts through the WHO to get at least one dose of vaccine in children in developing nations offer promise to replicate these encouraging results.

References: Meites E, et al, Significant declines in JORRP following HPV vaccine introduction in the US, Clin Infectious Dis, 73, 5, 2021 Novakovic D et al, A prospective study of the incidence of JORRP after iimplementation of a national HPV vaccination program, J Infect Dis 2018; 217; 208-12.

SS29 - HPV vaccination in vulnerable populations

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#7723

CANCER RADAR: ASSESS THE CURRENT AND (VACCINE) PREVENTABLE BURDEN OF CERVICAL CANCER AMONG INDIVIDUALS WITH A MIGRATION BACKGROUND ACROSS EUROPE

11 - Screening for women difficult to reach

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Background/Objectives: Approximately 12% (87 million people) of the European population has a migration background. The risk on cancers among migrants depends on the country-of-birth and the host-country of a migrant, and this risk can deviate markedly from the risk in the host population. Cancer RADAR aims to provide a Europe-wide quantification of infection-related and screening preventable cancers risk stratified by migration background. In the work presented here, we will focus on cervical cancer in Europe (1) establishing an infrastructure for data collection of (cervical) cancer stratified by migration background across Europe, (2) quantifying the fraction of women originating from a higher/lower risk area of cervical cancer when compared to the host population, and (3) estimating the expected burden of cervical cancer in the future and what fraction can be prevented.

Methods: Together with European cancer registries we are currently building an infrastructure to collect data on infection-related cancers and screening preventable cancers, including cervical cancer, stratified by migration background. Migration background is defined as a person living in another country than where he/she is born (birth-country). Furthermore, we will integrate UN International Migrant Stock1 and Global Cancer Observatory from IARC-WHO2, which allows us to estimate the fraction of women coming from an area at higher/lower risk for cervical cancer when compared to the host population. Next, we will adapt an existing statistical model created for young age-cohorts3 , to estimate the expected burden of cervical cancer among women with a migration background in Europe and estimate what fraction can be prevented through HPV vaccination.

Results: Cancer RADAR was launched during the Joint ENCR-IACR Scientific Conference in November 2023. Currently, there are 6 cancer registries involved in the piloting phase. We will expand cancer data collection stratified by migration background to other cancer registries in Europe in early 2024 and we expect to finish data collection in 2026. In a preliminary analysis, we have estimated that approximately 70% of women with a migration background living in Europe originate from an area where cervical cancer risk is higher than the average risk in Europe. These numbers highlight that a large proportion of women with a migration background may have health needs that differ from the host population.

Conclusions: Cancer RADAR's long-term goal is to improve the health outcome of cancers among individuals with a migration background in Europe.With this multidisciplinary approach we plan to establish an infrastructure that will provide policy makers with key analytical insights to develop evidence-based interventions, enabling cost-effectiveness assessment of tailored and targeted prevention strategies to improve health equity.

References: 1. United Nations, Department of Economic and Social Affairs. Population Division (2020). International Migrant Stock 2020 (United Nations database, POP/DB/MIG/Stock/Rev.2020). 2. Bray F, Colombet M, Aitken JF, Bardot A, Eser S, Galceran J, Hagenimana M, Matsuda T, Mery L, Piñeros M, Soerjomataram I, de Vries E, Wiggins C, Won Y-J, Znaor A, Ferlay J, editors (2023). Cancer Incidence in Five Continents, Vol. XII (IARC CancerBase No. 19). Lyon: International Agency for Research on Cancer. 3. Bonjour M, Charvat H, Franco EL, et al. Global estimates of expected and preventable cervical cancers among girls born between 2005 and 2014: a birth cohort analysis. The Lancet Public Health 2021; 6(7): e510-e21.

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#7824

Improving HPV vaccination coverage in the field: the case of Romania

10 - HPV screening

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Background/Objectives: This study addresses the critical issue of suboptimal HPV vaccination coverage in Romania, identifying challenges such as vaccine hesitancy, logistical barriers, and limited public awareness. Despite the proven efficacy of the HPV vaccine, understanding the nuanced factors influencing vaccination rates in Romania is imperative for developing targeted interventions.

Methods: Employing a mixed-methods approach, this study integrates quantitative analysis, qualitative insights, and a comprehensive literature review. Leveraging data from media tone analyses surrounding HPV vaccination, in-depth interviews with key stakeholders, and statistical assessments of vaccination rates, the research seeks to unravel the complexities contributing to vaccine hesitancy and coverage gaps.

Results: Preliminary findings illuminate the multifaceted landscape of vaccine hesitancy in Romania. Media tone analyses reveal prevalent misinformation and varying public sentiments, influencing perceptions of HPV vaccination. Stakeholder interviews underscore diverse factors contributing to hesitancy, including cultural beliefs and concerns about vaccine safety as well as more systematic barriers related to low vaccination coverage, such as the lack of national records of eligible participants, little involvement of family doctors, lack of specialised personnel to raise awareness regarding primary prevention at a community level, etc. Moreover, a notable finding is the role of social media in shaping public discourse on HPV vaccination. Analysis of online platforms indicates the potential for both positive and negative influences, highlighting the importance of strategic communication campaigns to counter misinformation. The study identifies key intervention areas such as educational campaigns, community engagement strategies and improvements in the healthcare infrastructure.

Conclusions: In conclusion, the study's findings underscore the intricate challenges influencing HPV vaccination coverage in Romania. The proposed interventions, grounded in a detailed analysis of media discourse, stakeholder perspectives, and statistical data, provide a nuanced and actionable roadmap. As Romania strives to overcome obstacles to vaccination, these evidence-based recommendations offer a targeted approach to boost coverage, ultimately contributing to the broader goal of reducing cervical cancer incidence in the country.

HN09 - HPV and Head & Neck Forum - Submitted papers III

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#6615

EVALUATION OF THE ATTRIBUTABLE FRACTION AND BURDEN OF HPV-RELATED OROPHARYNGEAL CANCERS IN GREECE-THE ORPHEAS STUDY

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The lack of robust epidemiological data in Europe on the attribution of HPV in oropharyngeal cancer (OPC) necessitates further investigation. This study evaluated the attributable fraction (AF) of HPV in OPCs in Greece.

Methods: ORPHEAS, a retrospective (medical charts review), observational, cross-sectional study with prospective recruitment, conducted in 8 reference hospitals in Greece, aimed to include 150 adult patients (pts) diagnosed with OPC between Q1 2017 and Q4 2022 who had a high-quality, treatment-naive tumor specimen. The primary endpoint was the AF of HPV in OPCs, as assessed by both p16 immunochemistry and HPV DNA PCR-DEIA-LiPA25 test (using SPF10 primers) by a central laboratory, among all OPC pts. Other endpoints described the pt characteristics at OPC diagnosis and assessed the HPV types for pts with HPV+ OPC with LiPA strips.

Results: A total of 147 pts were enrolled in the study (median age: 60 years; males, 113 [77%]; current smokers: 53 [36%]; former smokers: 51 [35%]). Most common anatomical sites of OPC tumors were the tonsils (71 pts, 48%) and the base of the tongue (53 pts, 36%). Of 110 (75%) pts with available tumor staging data, 20 (18%), 22 (20%), 25 (23%) and 43 (39%) were at stage I, II, III, and IV, respectively. Of 144 (98%) pts with available HPV status, the AF of HPV+ OPCs (combined positivity HPV DNA/p16) was 52% (75/144 pts; 95% confidence interval 44-60); of the remaining pts, 15 (10%) had HPV DNA+/p16−, 4 (3%) had HPV DNA−/p16+ and 49 (34%) had HPV DNA−/p16−. Overall, 73 (97%) patients were infected by an HPV type targeted by the 9-valent HPV vaccine (HPV16: 70 (93%); HPV18 and HPV58: 2 (3%) each type; HPV6 and HPV33: 1 (1%) each type). HPV+ pts compared to HPV- pts were younger (median age 58 vs 64 years; p=0.003); more likely to have tumors in the tonsils (65% vs 30%; p inf 0.001) and less likely to have tumors located in the base of the tongue (25% vs 46%; p=0.008); less likely to be current smokers (29% vs 48%), and more likely to be never smokers (33% vs 15%; overall p=0.022), with less smoking exposure (median of 34 vs 77 pack-years; p=0.016); and less likely to consume alcohol (25% vs 50%; p=0.005).

Conclusions: ORPHEAS showed a high (52%) AF of HPV in OPCs in Greece, approximating the AFs reported for Northern European countries. HPV+ pts were more commonly younger, non-smokers and non-alcohol consumers, with tumor location in the tonsils than HPV− pts. Since a significant number of OPC cases are preventable and impacting males, this study highlights a potential benefit of the recently introduced gender-neutral HPV vaccination in Greece.

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#6821

Incidence of oropharyngeal cancer in Brazil, data from the population-based cancer registries during 2000-2020

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oropharyngeal cancer (OPC) incidence is increasing worldwide, especially those associates with human papilloma virus (HPV) infection. However, incidence data on OPC and attributable fractions associate to HPV are scarce in Brazil due to lack of HPV prevalence and populational data. We aimed to estimate the OPC incidence in Brazil extracting data available from population-based cancer registries (PBCR) evaluating oropharyngeal subsites and incidence trends, according with the Brazilians regions.

Methods: OPC incidence data by age, sex, and anatomical subsites (CID-O 3) were obtained from 31 Brazilians PBCRs (https://www.gov.br/inca/pt-br) from 2000 up to 2020. Crude and age-standardized incidence rates were calculated using the Brazilian census 2010, provided by the Brazilian Institute of Geography and Statistics (IBGE), and the direct method adjusted by the world standard population. Average annual percent change (AAPC) was estimated thought the Joinpoint Regression Program software (version 4.7.0.0). Attributable fractions of HPV were calculated according to Azevedo, E. S. G., et al. (2016) with 14.4% for both genders. Nevertheless, as it is known that HPV prevalence for OPC is lower in females, attributable fractions obtained by de Martel, C., et al. (2017) were applied.

Results: There were 31 PBCRs with data available from all Brazilian regions, it covered 24% of the population mainly in the capitals. During a period from 2000 to 2020, a total of 15,648 OPC cases were registered. Males were most affected (81.7%) with 17.3% in the age group of 55 to 59 years. The oropharynx (40.6%) and subsites as base of tongue (24.9%), tonsil (22.6%), and uvula (11.9%) (P inf 0.05) were affected. The highest incidence rates of OPC were observed in Southeastern and Southern regions, ranging from 3.1 to 9.4/100,000 in males. OPC in men presented an increasing trend with a statistically significant AAPC in Manaus (4,8 CI: 3.0/7.8), Palmas (10,3 CI: 8.5/15.9), Fortaleza (5,3 CI: 3.6/7.7), Recife (5,7 CI: 3.9/9.0), Campo Grande (4,8 CI: 2.4/7.2), Belo Horizonte (4,8 CI: 3.8/6.3), Vitória (6,1 CI:3.7/9.9), and Curitiba (2,3 CI:1.0/3.9). Females presented increasing trend in three regions of the northeast and five regions of the southeast, with statistically significant AAPC. HPV-attributable fractions for 24% of the population showed 1,841 cases in males and 411 OPC cases in females.

Conclusions: OPC incidence in Brazil is low, however, the rates vary depending on the Brazilian region. Incidence trends are increasing in half of Brazilian regions for male and female. OPC attributed to HPV were relatively few, nevertheless, comprehensive studies are still needed on HPV prevalence in OPC by Brazilian regions.

References: Azevedo, E. S. G., de Moura, L., Curado, M. P., et al. (2016). The Fraction of Cancer Attributable to Ways of Life, Infections, Occupation, and Environmental Agents in Brazil in 2020. PLoS One, 11(2), e0148761. de Martel, C., Plummer, M., Vignat, J., & Franceschi, S. (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer, 141(4), 664-670.

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#6849

AUSTRALIAN POPULATIONS' ATTITUDES AND KNOWLEDGE OF OROPHARYNGEAL HPV INFECTION

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: As the incidence of oropharyngeal squamous cell carcinoma (OPSCC) increases, knowledge of the population about HPV transmission, risk factors, attitudes to testing in dental settings and discussing relevant sexual health topics with treating dentists play an important role in the screening and diagnosis. Our study aimed to investigate Australian populations' attitudes and knowledge of HPV infection and assess dentists' potential role as educators for HPV.

Methods: The project was designed as a mixed-method study consisting of a cross-sectional survey and patient interviews. In the quantitative part, adult members of the Australian population ≥ 18 years were recruited from all over Australia and invited to complete an online survey distributed through Facebook. The data was analysed using SPSS version 24.29. Descriptive statistics such as mean and standard deviation for continuous variables and frequency and percentage for categorical variables were calculated and tabulated, and X2 was used for bivariate analysis. A p-value ≤.05 was considered significant. The qualitative arm involved interviewing participants recruited from a Sydney private dental surgery. Face-to-face interviews with 30 participants were recorded and transcribed. Thematic analysis was conducted.

Results: In total, 273 participants responded to the cross-sectional survey; 181 (66.3%) were females, and 117 (42.9%) were born in Australia. The majority displayed fair awareness of HPV infection, associating it with warts (n=164; 60.1%), throat cancer (n=107; 39.2%) and cervical cancer (n=105; 38.5%). However, 46 respondents (16.8%) were unsure what it was. Younger participants (20-29 years) were significantly less knowledgeable about HPV infection than those 60 years or older (p=0.03). Males were more unsure of the purpose of the HPV vaccine compared to females (p=0.02), and they were also less aware of HPV as a potentially cancer-causing factor(p=0.002) and of the HPV vaccine as a cancer prevention method (p=0.003). Those who had been vaccinated against HPV identified more correct responses regarding HPV compared with those who were not vaccinated (p=0.01). Of the 30 participants interviewed, only six displayed fair knowledge of HPV. The rest did not know what it was (11) or were unsure. Eleven participants associated HPV with sexually transmitted infections. Six participants were aware of the association between HPV and cervical cancer, and five linked the infection with oropharyngeal infection. The majority (20) approved of discussing relevant sexual health topics with their treating dentists. Twenty-four participants approved of testing for HPV in dental surgery.

Conclusions: The survey highlighted overall poor general knowledge of HPV infection, especially among females and older participants. The qualitative study mirrored these findings. Our study showed that participants were receptive to discussing HPV infection and relevant sexual health topics with their dentist. The increasing incidence of OPSCC warrants more efforts to improve the population's awareness of oral HPV infection and sexual behaviour as risk factors. Since patients view dental practitioners as health care providers and approve of discussing sexual behaviour and other risk factors associated with OPSCC with them, dental professionals are ideally placed to provide initial screening for oral HPV infection.

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#6934

Burden of Human Papillomavirus related to oropharyngeal cancers in European countries: The BROADEN study results

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oropharyngeal cancers (OPC) associated with Human Papillomavirus (HPV) have emerged as a significant public health concern over time, especially in males. Recent studies from the United States reveal that OPC has now surpassed cervical cancer as the most common HPV-related malignancy. Despite these trends, the availability of data on HPV-driven OPC and genotype distribution in Europe is limited. This study aims to estimate the HPV attributable fraction (AF) of OPC and assess the AF trends in the last 10-year period.

Methods: BROADEN, a non-interventional study of HNC patients diagnosed in 2008-2009 and 2018-2019, was conducted in France, Germany, Italy, Portugal, and Spain. The study included adult patients with a first primary diagnosis of OPC during the two defined study periods and with a pre-treatment tumor tissue sample available. HPV was tested in a central laboratory using a combination of the following approaches: p16INK4a immunohistochemistry, HPV-DNA PCR, and HPV E6*I mRNA. HPV attributability is defined for those patients with HPV positivity in at least two tests.

Results: Results presented here focus on Spain and Portugal only. Results for France, Germany and Italy will be available early 2024 (HPV testing is ongoing). Overall, in Spain and in Portugal, 526 patients diagnosed with OPC were included in the study across 21 oncology hospitals (17 in Spain and 4 in Portugal). A total of 483 valid samples were tested for HPV (197 samples from 2008-2009 and 286 from 2018-2019). Eighty-two% of the OPC patients were male, mean (SD) age at OPC diagnosis was 61 years (10.5), 57% were current smokers, 30% ex-smokers, and 38% were heavy alcohol consumers (male >4 and female >3 drinks per day). For the 2008-2009 period, HPV AF was 8.1% (95%CI=4.7%-12.9%) and was 23.1% (95%CI=18.3%-28.4%) for the 2018-2019 period, corresponding to an annual percentage change of 11.1%. Using only p16INK4a as surrogate to define HPV attributability, 25.7% of false positive results were obtained (28/109). From HPV attributable samples, 92.7% (n=76) presented high-risk HPV genotypes included in 9-valent vaccine (16, 18, 31, 33, 45, 52 and 58) with HPV16 genotype as the most prevalent (86.6%).

Conclusions: Study findings in Spain and Portugal demonstrate a statistically significant increase of HPV-driven OPC from 8.1% to 23.1% over the 10-year period (2008-2009 to 2018-2019). This increase confirms the trend of HPV AF observed in OPC in several high-income countries. The incidence of these cancers is expected to continue to rise over the future decades until the effects of the HPV gender neutral vaccination programs are realized.

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#6714

Burden of adult-onset recurrent respiratory papillomatosis: a systematic literature review

39 - Public health

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Background/Objectives: Adult-onset recurrent respiratory papillomatosis (AoRRP) is a severe recurrent disease caused by human papillomavirus (HPV), mainly caused by HPV6 and HPV11, and characterized by the development of papillomas in the respiratory tract. The aim of this study was to assess the published evidence regarding the disease clinical, epidemiological, and economic burden of AoRRP.

Methods: A systematic literature review (SLR) was conducted according to the Cochrane Group and PRISMA guidelines. MEDLINE, Embase and Cochrane Library databases and conference proceedings published in last 4 years were searched. The outcomes of interest were clinical (i.e., patient characteristics, risk factors, symptoms, treatment, and procedures), humanistic, epidemiological (i.e., incidence, prevalence, genotype, recurrence frequency, and mortality) and economic (i.e., costs, indirect costs, resource use) related endpoints.

Results: A total of 48 publications were included for analysis; 25 clinical, 7 humanistic, 5 epidemiologic, and 11 economic burden full-text articles. The major contributors to the clinical AoRRP burden are the frequent surgeries and disease-related symptoms impacting the voice and airway (hoarseness/loss of voice, stridor, rapid/difficult breathing, chronic cough, and difficulty swallowing). AoRRP patients may require multiple surgical disease debridement, and there are no approved systemic adjuvant therapies to prevent/delay recurrence. These patients have more voice problems and a lower general health perception compared to general population. The treatment costs varied by treatment options, frequency and country. Due to the recurrent nature of AoRRP, the humanistic and economic burden is significant.

Conclusions: Limited AoRRP data are available for this high morbid and devastating disease. Reported disease management costs are likely underestimated due to "outdated" treatments costs and limited projections to lifetime. Further research is necessary to obtain more robust data that will help address the information gap in the global clinical, humanistic, epidemiological, and economic burden.

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#7134

JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS - INSIGHTS INTO NATURAL HISTORY AND RISK FACTORS FOR AGGRESSIVE DISEASE

03 - Epidemiology and natural history

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Background/Objectives: Although Juvenile Onset Recurrent Respiratory Papillomatosis (JoRRP) is considered a rare disease in developed countries, reports from LMICs including Southern Africa suggest that the incidence and prevalence of JORRP is relatively higher. Due to the life-threatening risk of upper airway obstruction, patients require frequent surgical excisions and debulking of papillomas. In South Africa, there is a disproportionately high prevalence, 1.34-3.88 per 100,000 children, compared to 1.7-2.6 per 100,000 children in the United States. This South African prevalence is probably an underestimation due to reporting inconsistencies and a shortage of Otorhinolaryngology specialist services. We sought to describe the demographic patterns of JORRP in the Kwa-Zulu Natal (KZN) province of South Africa and characterize factors associated with aggressive disease.

Methods: Data was extracted from electronic Medical Records from Inkosi Albert Luthuli Central Hospital, the quaternary care center at which the majority of surgical debulkings occur in the public sector in KZN. The records of all JoRRP patients who received surgical intervention between 2012 and 2023 were included for analysis. Data recorded include geographical district, race, gender, papilloma histology, surgical trend, extra-laryngeal extension of disease, disease complications and overall disability score.

Results: 276 JoRRP patients were included in the analysis. 155 (56.2%) were male and 121 (43.8%) were female. 269 (97.5%) were Black African, 2 (0.7%) were Indian/Asian, 1 (0.4%) were Coloured, and 4 (1.4%) were Other/Unknown. 119 (43.1%) were receiving some form of social support state grant. Dysplasia was present in 67 (24.3%) patients. Extra-laryngeal disease was present in 139 (50.4%) patients. Only 19 (6.8%) required tracheostomy and 12 (4.3%) required intubation to maintain airway. During the year of the highest surgical trend, the average number of debulking surgeries performed was 3.69/year, with a range of 1 to 23. The year of highest surgical trend occurred an average of 1.68 years after the initial diagnosis. Multiple logistic regression revealed that age at onset ($OR = 0.88$, $p < 0.001$) and years since diagnosis of last surgery ($OR = 1.17$, $p < 0.001$) were associated with aggressive disease, as defined by either requiring more than 3 surgical debulkings per year, extra-laryngeal involvement, requiring tracheostomy, or intubation. Aggressive disease was associated with an increased number of complications compared to non-aggressive disease ($p = 0.009$).

Conclusions: This study presents one of the largest single-center JoRRP cohorts in recent medical publication history. JoRRP is a serious disease that places a high burden on the population and health services of KZN. Younger age at disease onset and longer years since diagnosis of last surgery were both associated with aggressive disease. Aggressive disease was associated with an increased number of complications compared to non-aggressive disease. However, dysplasia was not associated with aggressive disease. This finding presents a clinical paradox, not previously well-described nor understood. A separate prospective study is underway to analyse the role of underlying co-infections, co-morbidities and HPV genotype in disease severity. The large cohort size will enable critical insights for health system adaptation for improving the management of children with HPV-related disease.

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#6483

Prevalence of oral human papillomavirus infection among the general adult population in Hong Kong

28 - Oral HPV infection

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Background/Objectives: Epidemiologic characteristics of oral human papillomavirus (HPV) infection in Chinese remains relatively unexplored. This study aimed at elucidating more information to assist public health planning for the control of the associated oropharyngeal cancer.

Methods: A cross-sectional study in 2021-2023 collected oral rinse gargle samples from a HPV vaccine-naïve general adult population in Hong Kong. Samples were tested for HPV DNA by a PCR-based method. Epidemiologic information including sociodemographic, health, life style, and sexual behavior were collected by a self-administered standardized questionnaire.

Results: Altogether, 2323 subjects aged 18-75 years with even gender and age distribution were recruited. The overall prevalence for oral HPV infection with all types combined was 1.5% (95% CI: 1.05-2.04), with high-risk and non-high-risk types were both 0.7% (0.46-1.17), and without significant difference between genders. The prevalence increased with age, and that of women peaked at 45-54 years, whereas it continued to rise in men. Within the age group >64 years, the prevalence among men was significantly higher than that of women for Any-HPV infection. HPV52 was the most commonly detected type. Univariate analysis revealed more lifetime sexual or oral sexual partners as risk factors, whereas higher educational level had an independent protective effect.

Conclusions: Risk of oral HPV infection or/and persistence increases with age for both sexes in general adult population in Hong Kong. The government should be prepared for the increase in health burden associated with oral HPV infection associated diseases, particularly oropharyngeal cancer. It is worthwhile to reassess the current HPV vaccination strategy towards to a gender-neutral one considering the local epidemiology data

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#6753

Oral Human Papillomavirus prevalence and risk factors among healthy populations in France, Germany, Spain, the United Kingdom and the United States: Results from the PROGRESS (PRevalence of Oral hpv infection, a Global aSSessment) study

28 - Oral HPV infection

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Background/Objectives: HPV-related oropharyngeal cancer (OPC) is increasing in incidence yet little is known about oral HPV infection in the general population. This study assessed oral HPV prevalence and associated factors among a general population in Europe and the United States (US).

Methods: Between November 2020 and June 2023, adults aged 18 to 60 were recruited from dental offices in France, Germany, Spain, the United Kingdom and US. Participants completed sociodemographic and behavioral questionnaires and provided oral rinse and gargle specimen. HPV-DNA detection and genotyping was performed via the SPF10/DEIA/LiPA25 system in two central laboratories. Dentists provided information on oral health and collected self-reported HPV vaccination status.

Results: Of 7,667 participants, 45.7% were males, the median age was 40 and 9.2% reported having received an HPV vaccine. Oral HPV prevalence was 7.2% for any genotype and 2.0% for HR genotypes. Prevalence was significantly higher among males vs females (9.8% vs 5.0%; pinf0.0001). Among positives the most prevalent genotypes were 16 (8.2%) and 51 (5.4%). There were 37 co-infections. Factors significantly associated with oral HPV prevalence in bivariate analysis included participant sex, age, smoking status, lifetime number of female oral sex partners, and presence of periodontal disease.

Conclusions: Oral HPV burden was highest among older men who may be at risk of developing OPC.

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#6895

PERSISTENT ORAL HIGH-RISK-HPV-INFECTIONS AND HERPESVIRUSES CO-INFECTIONS

28 - Oral HPV infection

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Background/Objectives: Oncogenic high-risk human papillomavirus (HR-HPV) infections play an etiological role in a subset of oral squamous cell carcinomas (OSCCs). That is, only a fraction of OSCCs are induced by oncogenic HPVs, and eventually only a few persistent oral HR-HPV-infections will develop into OSCCs. One possible cancer-driving factor is co-infection with other viruses. Here we assessed oral viral co-infections in persistent oral and progressive cervical HPV infections and compared to individuals with transient or without oral HPV infections.

Methods: This study included 43 women from the prospective Finnish Family HPV (FFHPV) - study conducted at the University Hospital of Turku, Finland between the years 1998-2007. This study used the saliva samples that were collected at baseline and at 12-, 24- and 36-months follow-up visits. Saliva samples were deep sequenced with the illumine platform. Women were further stratified to the following groups: 1) persistent oral HR-HPV infections (N=8), 2) transient or no oral HR-HPV infections (N=26) and 3) women with cervical disease progression to high-grade intraepithelial lesion (HSIL) during the follow-up (N=9). Targeted mapping of known human herpesviruses from the metagenomes was performed.

Results: Moderate to high coverage viral signal for human alphaherpesvirus 1 (0%), human betaherpesvirus 6B (2.3%), human betaherpesvirus 7 (60.5%) and Epstain-Barr virus (EBV) (41.9%) was detected among the 43 women. When stratified into persistent and non-persistent oral HR-HPVs infected women for each follow-up time point we observed no significant association with any tested virus among women without oral HR-HPVs infections compared to women with persistent oral HR-HPV infections or women with malignant cervical transformations.

Conclusions: We observed no association between any of the herpesvirus infections tested and the oral HR-HPV persistence status in women. Further work is warranted to elucidate the possible role of other viral co-infections in the risk of developing HR-HPV induced OSCC.

SS33 - PERCH (PartnERship to Contrast HPV): European joint action aiming for improved HPV vaccination coverage and data collection

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#7927

SS 33 - Dissemination strategies to increase HPV awareness among the target population

06 - HPV prophylactic vaccines

Background/Objectives: Cervical cancer remains a major public health problem in Europe. The Joint Action Project PERCH (European Partnership to Contrast HPV) addresses this through dissemination and communication strategies aimed at increasing awareness of HPV in the target population, also young people, parents, teachers and healthcare workers. Funded by the European Union, PERCH is a collaborative project involving 18 European countries and 34 partner organizations aiming to implement HPV vaccination objectives set by the Europe's Beating Cancer Plan. Aligned with the WHO's "90-70-90" strategy, PERCH strives for at least 90% HPV vaccine coverage among girls and boys by age 15.

Methods: PERCH emphasizes multi-stakeholder engagement, involving policymakers, healthcare professionals, educators, community leaders, and civil society organizations. The project implements national toolboxes, actions, media campaigns, and educational support to healthcare professionals, embedded in national or regional communication plans. A Governmental Advisory Board (GAB) established through the project ensures sustainability, providing feedback, policy guidance, and contributing to integration and sustainability plans among the participating countries/ecosystems/partners.In order to promote cross-border peer support and partnerships with related projects such as EU-Vax, PROTECT-EUROPE, RIVER-EU, and ReThinkHPVaccination, PERCH relies on an extensive international network.

Results: Short-term outcomes include improved information on implementation, increased awareness among target groups, stronger stakeholder networks, and empowered countries to procure vaccines efficiently. Another dissemination strategy is tactical used of social media through which Project PERCH actively disseminates information. Slovenia is actively involved and leads efforts to identify and engage stakeholders, develop guidelines for communication strategies, and disseminate project's and partners' best practice examples. Stakeholder mapping has identified 281 relevant entities, guiding actions outlined in the Communication and Dissemination Plan, available on the PERCH website repository. Key communication tools include newsletters, key messages, and infographics. The establishment of PERCH communication and dissemination working group facilitates collaboration, with regular online meetings involving 64 members from all partner countries. The HPV Vaccination Guild promotes voluntary mobilization of HPV vaccination supporters, sharing of knowledge, experience and ideas through workshops and webinars, fostering international collaboration. In order to further develop the existing HPV-related messages and materials, we are developing PERCH social media strategy with key messages for parents and young people targeted by vaccination that will be adapted and tailored by project partners to national context. This work will directly inform the development of infographics for use in social media campaigns, as well as the guidelines for the communication strategies that aims to enhance consortium members' capacity to plan and deliver effective communication plans.

Conclusions: The project's contribution to closing the gap in HPV vaccination coverage aligns with the overarching goal of eliminating unacceptable cervical cancer disparities across Europe.

References: More information about the PERCH project: https://www.projectperch.eu/

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#7775

Implementation of HPV vaccination in Europe

06 - HPV prophylactic vaccines

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Background/Objectives: To meet WHO's 90% coverage target for HPV vaccination by 2030, actions are needed by countries to improve their specific vaccination coverages. Our study aims at describing the scenarios currently implemented to contact and reach the target population and administer the HPV vaccines, assessing barriers, facilitators and solutions that impede/improve access to HPV vaccination, identifying weaknesses in the supply-administration chain and describing the general process of collection and compilation of HPV vaccination data. This study is part of the Project PERCH (PartnERship to Contrast HPV), a European Joint Action, which involves 34 organisations from 18 Member States (MSs) for a duration of 30 months. (Grant Agreement: 101075314)

Methods: The following study is the analysis of a questionnaire completed by the 17 MSs partnering in PERCH. The questionnaire, developed through one-hour input sessions and pilot-tested, consists of six modules and 41 main questions covering various aspects of HPV vaccination: 1) procurement and logistical chain of HPV vaccines; 2) information on the HPV vaccination system; 3) procedure regarding vaccination consent and information; 4) barriers and enablers of participation in HPV vaccination; 5) data registration, data processing and data linkage; and 6) suggestions for PERCH pilot actions/campaigns. Analysis involved clarifying unclear responses, conducting statistical analysis of quantitative data using STATA/SE 16.0, and processing qualitative data using QSR Nvivo 14 software.

Results: As of August 2023, all PERCH MSs have integrated the HPV vaccine into their immunisation programmes. Sixteen countries with routine HPV vaccination follow a gender neutral approach, except Estonia, which is considering the inclusion of boys in the target group for 2024. Catch-up HPV vaccination strategies vary across PERCH MSs, including both genders in some countries (BE, HR, FR, DE, GR, NO, SI) and restricting to girls in others (ES, IT, LT, EE). Invitations and reminders vary, with some countries having organised systems, often school-based, while others rely on healthcare providers (HCPs)' initiatives. In total, 11 countries do invite the target population, while only 5 reported having no organised invitational system in place. Opportunistic activities vary in terms of additional actions to boost coverage, sometimes offering vaccination outside the regular programme in specific settings or for certain populations. Most countries offer vaccines free of charge directly at healthcare practices/school-based settings or patients can purchase it through pharmacy (partially or fully reimbursed or not), but only a few can link HPV vaccination registries with other registries (screening, cancer, morbidity). Primary care centers, school-based health centers, and private practices are key sites for HPV vaccine delivery, with school settings playing a pivotal role in many countries.

Conclusions: The answers from the questionnaire form a comprehensive resource on HPV vaccination implementation. It has generated pertinent suggestions for improving HPV vaccination services by comparing and improving various aspects of vaccine delivery, infrastructure, policies, and data monitoring among MSs. The suggestions provided can be grouped into four main categories: improving access to vaccination, enhancing education and awareness, strengthening monitoring efforts, and fostering collaboration among multiple stakeholders, including HCPs, community leaders, and parents.

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EFFECTIVENESS OF HPV VACCINATION WITH ONE DOSE

06 - HPV prophylactic vaccines

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Background/Objectives: Vaccination against HPV is one of the key actions to prevent cervical and other HPV-related cancers in women and men. Up to now, two-to-three doses of HPV vaccines, depending on age, are recommended in most countries. Demonstrating effectiveness of one-dose of HPV vaccination may trigger an enormous acceleration of WHO's aim to reach 90% worldwide HPV vaccination among girls before the age of 15. Moreover, it is important to assess whether adolescents having missed one dose are sufficiently protected. Therefore, we investigated the efficacy/effectiveness of one versus no dose of HPV vaccination in a systematic review in the framework of the European Joint Action project "PartnERship to Contrast HPV' (PERCH, https://www.projectperch.eu/) that contributes to the implementation of Europe's Beating Cancer Plan that aims to support Member States' efforts in the alignment with the WHO's '90-70-90' strategy.

Methods: The literature search revealed a key review by Cochrane Response. Building upon this, a search was performed to retrieve new publications. Randomized clinical trials (RCTs) studies and observational studies were included. The target population consists of females and males, without age restrictions, who were vaccinated with no, one or more than one dose of HPV vaccine. Bi-, quadri- and nonavalent HPV vaccines were included, with no restrictions on brand. Both clinical (cervical intraepithelial neoplasia of grade 2 or worse [CIN2+], CIN3+, cervical cancer, genital warts and abnormal cytology) and virological endpoints (incident, prevalent and persistent HPV infection) were assessed. Random effect models were used for meta-analytical pooling of ratios with study type (RCT or observational study) and vaccine brand as stratifying variables.

Results: Five-hundred and fifty studies were found, and after filtering those with efficacy/effectiveness results 152 studies remained. No additional references were found when searching by hand. On the WHO International Clinical Trials Registry Platform, 1704 trials were found using the term "HPV'. One-hundred ninety-nine trials had results and none of them had relevant data. One dose of HPV vaccine, regardless of the vaccine brand, protected better than no dose for the outcomes CIN2+, CIN3+, genital warts (only documented for Gardasil), incident HPV infection (16/18, 6/11, 6/11/16/18), prevalent HPV infection (16/18) and persistent HPV infection (16/18 and 16/18/31/33/45/52/58). RCTs and observational studies with one dose of Gardasil demonstrated higher efficacy and effectiveness than no dose, while observational studies with two doses of Cervarix showed higher effectiveness than one dose for the development of CIN2+ and CIN3+. The bivalent Cervarix vaccine demonstrated better protection against incident (cross-reacting) HPV31/33/45 infection compared to no dose in RCTs. In RCTs, protection against persistent HPV16/18 infection was similar for one dose of Cervarix and Gardasil compared to no dose. Higher protection of Gardasil against persistent HPV16/18/31/33/45/52/58 infection was documented in a RCT.

Conclusions: This review demonstrated protection against targeted and cross-reacting HPV infection and related disease of one dose of HPV vaccine compared to no dose, confirming findings of the Cochrane Response review. The next steps of our review is to include new studies as soon as published and to include also per protocol findings of trials as well as immunogenicity data.

SS35 - Present status of genome-wide association studies

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Polygenic risk scores for cervical malignancies

21 - Artificial intelligence - Big data - Machine learning

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Background/Objectives: Genome-wide association studies (GWASs) are a valuable tool to describe the genetic basis for common human diseases, and in line with this, they have also identified susceptibility loci for cervical cancer and other related cervical pathologies. Polygenic risk scores (PRSs) combine the effects of several genetic variants into one variable that can be used to assess the genetic risk of a disease for an individual. Therefore, PRSs can be used to group participants into different risk categories for disease and are also used as a covariate in epidemiological analyses.

Methods: We construct a PRS for cervical cancer, assess its risk stratification ability and associations with cervical cancer, cervical dysplasia and high-risk HPV infection. Finally, we evaluate the pleiotropic phenomic network associated with genetic risk for cervical cancer.

Results: We found the developed PRS is associated with cervical cancer [hazard ratios (HR) = 3.1 (1.7-5.6) for the top 15% vs lowest 15% of individuals]. While on average, approximately 1% of women in our dataset were diagnosed with cervical cancer by the age of 70, women in the highest five percentiles of our tested PRS reached the same cumulative risk level by age 55, 15 years earlier. Similarly, on average, approximately 30% of women in our dataset were diagnosed with cervical intraepithelial neoplasia by the age of 70, but women in the top 20% of genetic risk reached the same cumulative incidence before their 40th birthday. The calculated PRS was also associated with other HPV- and immune-system-related diagnoses in a phenome-wide association study analysis.

Conclusions: Our results suggest cervical cancer PRS could be an additional tool for cervical cancer risk stratification, either for screening or scientific research.

References: Tisler A, Uusküla A, Ojavee SE, Läll K; Estonian Biobank research team; Laisk T. Polygenic risk scores for cervical HPV infection, neoplasia and cancer show potential for personalised screening: comparison of two methods. Infect Agent Cancer. 2023 Dec 7;18(1):82. doi: 10.1186/s13027-023-00561-4. PMID: 38057845; PMCID: PMC10702115. Koel M, Võsa U, Jõeloo M, Läll K, Gualdo NP, Laivuori H, Lemmelä S; Estonian Biobank Research Team; FinnGen; Daly M, Palta P, Mägi R, Laisk T. GWAS meta-analyses clarify the genetics of cervical phenotypes and inform risk stratification for cervical cancer. Hum Mol Genet. 2023 Jun 5;32(12):2103-2116. doi: 10.1093/hmg/ddad043. PMID: 36929174; PMCID: PMC10244231.

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GWAS signals for cervical cancer and HPV type

25 - Cervical neoplasia

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Background/Objectives: Persistent infection by high-risk human papillomavirus triggers the development of cervical cancer and dysplasia. Hereditary risk factors from genome-wide association studies (GWASs) for cervical cancer have identified multiple genomic variants at the human leukocyte antigen (HLA) locus (6p21.32-33) containing genes with an essential role in modulating host immune response, as well as variants on chromosome 2 (PAX8), 5 (near CLTPM1L) and 17 (GSDMB). Recent HPV seropositivity GWASs for HPV seropositivity have identified HPV-type specific genomic variants at chromosome 6 (HLA) and chromosome 14 (near VASH1).

Methods: We tested these genomic variants in the German Cervigen case-control series of invasive cervical cancer, dysplasia, and healthy controls. We further investigated the functional relevance of these variants by expression quantitative trait loci (eQTL) analysis in cervical tissues.

Results: We replicated risk loci at HLA, PAX8 and GSDMB, and we find evidence that HPV seropositivity variants at chromosome 6 and 14 may modulate type-specific cervical cancer risk. rs9357152 may exert its effect through regulating HLA-DRB1 induction in the presence of HPV. Finally, we analyze HPV-type specific signals from the German Cervigen GWAS and provide supportive evidence of replication for additional cervical cancer risk loci.

Conclusions: In summary, we propose that several additional risk loci exist for cervical dysplasia and cancer, and some of them may be HPV-type specific.