EUROGIN 2021 ABSTRACTS

FREE COMMUNICATIONS SESSIONS

FC01 - Management I

#2263

59 - Risk management

CLASSIFICATION OF HIGH-GRADE CIN BY P16, KI-67, HPV E4 AND FAM19A4/MIR124-2 METHYLATION STATUS DEMONSTRATES CONSIDERABLE HETEROGENEITY WITH POTENTIAL CONSEQUENCES FOR MANAGEMENT

Vink F[1], Dick S[2], Heideman D[3], De Strooper L[4], Steenbergen R[5], Lissenberg - Witte B[6], Floore A[7], Bonde J[8], Oštrbenk Valenčak A[9], Poljak M[10], Petry K[11], Hillemanns P[12], Van Trommel N[13], Berkhof J[14], Bleeker M[15], Meijer C[16]

[1]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, De Boelelaan 1117 , Amsterdam, Netherlands

[2]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, De Boelelaan 1117 , Amsterdam, Netherlands

[3]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[4]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, De Boelelaan 1117, Amsterdam, Netherlands

[5], Amsterdam, Netherlands

[6]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Epidemiology and Data Science, Amsterdam, Netherlands

[7]Self-screen B.V., Amsterdam, Netherlands

[8]Molecular Pathology Laboratory, Department of Pathology, Hvidovre Hospital, Hvidovre, Denmark

[9]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[10]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[11]Department of Gynecologic Oncology, Klinikum Wolfsburg, Wolfsburg, Germany

[12]Department of Obstetrics and Gynaecology, Hannover Medical School, Hannover, Germany

[13]NETHERLANDS CANCER INSTITUTE, Amsterdam, Netherlands

[14]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[15]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, De Boelelaan 1117, Amsterdam, Netherlands

[16]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Leiden, Netherlands

Background/Objectives: High-grade cervical intraepithelial neoplasia (CIN2 and CIN3) represent a heterogeneous disease with varying cancer progression risks. In current practice, all CIN3 and the majority of CIN2 lesions are treated in order to prevent progression to cervical cancer. However, spontaneous regression of CIN2 and CIN3 naturally occurs, yet if treated as per current guidelines this would constitute overtreatment. Biomarkers indicative for a productive human papillomavirus (HPV) infection (HPV E4), a transforming HPV infection (p16 and host-cell DNA methylation) and cellular proliferation marker (Ki-67) could provide guidance for clinical management in women with high-grade CIN.

Methods: An international, multicentre, post-hoc study was designed within 5 European prospective referral or HPV-based screening cohorts to assess biomarker patterns in a large series of 262 CIN2 and 235 CIN3. The cumulative score of immunohistochemical expression of p16 (score 0 - 3) and Ki-67 (score 0 - 3), referred to as the "immunoscore' (IS), immunohistochemical HPV E4 expression and FAM19A4/miR124-2 methylation in the corresponding cervical scrape were evaluated.

Results: In the total group of CIN2/3 lesions, 30 lesions were classified as IS group 0 - 2 (6.0%), 151 lesions as IS group 3 - 4 (30.4%) and 316 lesions as IS group 5 - 6 (63.6%). Increasing p16 and Ki-67 expression was associated with increasing CIN grade. E4 expression decreased significantly from CIN2 to CIN3 ($p<0.001$) and with increasing immunoscore group ($ptrend<0.001$). Methylation positivity increased significantly from CIN2 to CIN3 ($p<0.001$) and increasing immunoscore group ($ptrend<0.001$). E4 expression was present in 9.8% of CIN3 (23/235) and in 12.0% of IS group 5 - 6 (38/316). Notably, in a minority (43/497, 8.7%) of high-grade lesions characteristics of both a transforming HPV infection (hypermethylation) and productive HPV infection (E4 expression) were found simultaneously, confirming heterogeneity within high-grade CIN lesions. Based on the presumed short term cancer risk of the biomarkers used mainly methylation was found to harbour prognostic information.

Conclusions: We found a considerable amount of heterogeneity in biomarker expression in a large series of high-grade CIN lesions, evaluated with p16, Ki-67 and E4 immunohistochemical staining and FAM19A/miR124-2 methylation. Biomarker profiles were defined that might help the clinician in a more personally tailored management of women with high-grade CIN thereby preventing overtreatment, especially in young women.

#2194

59 - Risk management

RISK OF CIN3+ IN HPV-POSITIVE WOMEN WITH NORMAL CYTOLOGY AND FIVE-YEAR TYPE CONCORDANCE: A RANDOMIZED COMPARISON

Inturrisi F[1], Bogaards J[2], Heideman D[3], Meijer C[4], Berkhof J[5]

[1]AMSTERDAM UMC - VUMC, Amsterdam, Netherlands

[2]Amsterdam UMC - VUmc, Amsterdam, Netherlands

[3]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[4]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Leiden, Netherlands

[5]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

Background/Objectives: In the context of HPV-based cervical cancer screening programs, management of HPV-positive women with normal cytology is debated. HPV persistence over consecutive screening tests may be used for risk stratification of these women.

Methods: To demonstrate the potential of five-year HPV type persistence as a disease marker for HPV-positive/cytology-negative women, we assessed the risk of cervical intraepithelial grade 3 or worse (CIN3+) after repeatedly testing positive for the same HPV type(s). We used data of two HPV-based screens five years apart from the randomized population-based screening study Amsterdam (POBASCAM). We compared 18-month CIN3+ risks in HPV-positive women (intervention group, n=1066) to those in HPV-positive/cytology-negative women who tested HPV-positive in the next screening round (control group, n=111) five years later, stratified for HPV type concordance.

Results: HPV-positive women of the intervention group had an 18-month CIN3+ risk of 15%, while those of the control group had a risk of 40% after two-round type concordance (relative risk 2.6, 95% confidence interval 1.9-3.4) and of 20% after type switch (1.3, 0.5-3.2). The relative increase in CIN3+ risk after two-round type concordance was high both in HPV-positive women who tested positive for the types 16/18/31/33/45 (1.8, 1.3–2.5) and also in those who tested negatives for those types (9.9, 4.4-21.9) in both rounds.

Conclusions: Women with five-year HPV type concordance have a high CIN3+ risk warranting immediate referral for colposcopy, also for less aggressive high-risk HPV types. In HPV-based screening programs, the use of repeat HPV genotyping after five years would translate into a reduced demand of adjunct cytology testing.

#2167

60 - Triage of HPV positive women

OPTIMAL PERFORMANCE SPECIFICATIONS FOR TRIAGE TESTING OF PRIMARY HPV-POSITIVE SPECIMENS

Andrews J[1]

[1]BD, Sparks Glencoe, United States

Background/Objectives: Primary HPV testing is preferred for cervical screening, compared to cytology because of the superior sensitivity and high negative predictive value for CIN2+. However, most HPV infections are productive infections, and not transforming. Therefore, a triage test is required to distinguish HPV-positive women with clinically relevant cervical lesions from those with transient infections. Among HPV-positive women, the twin goals for triage, that must be balanced, are safety and burden. As a screen-triage program, the safety metric is negative predictive value (NPV) for CIN3+. The burden of screen-triage is measured by the proportion of colposcopies (minimize the number of avoidable colposcopies). As a triage test property, the higher the specificity, the better reduction of burden. As a screen-triage program, the burden metric is positive predictive value (PPV) for CIN3+. NPV and PPV vary with the prevalence of high-grade CIN in HPV-positive women in the screening program. Countries express different guidance for the balance of safety and burden. Alternative triage tests to improve risk stratification and prognosis include cytology, genotyping, immunohistochemical staining, DNA methylation, viral methylation, and oncoproteins.

Methods: A literature survey and extraction was completed for studies reporting performance of triage tests for primary HPV-positive specimens (sensitivity (Sn), specificity (Sp), PPV, NPV), for cytology, genotyping, immunohistochemical staining, DNA methylation, and viral methylation.

Results: The prevalence of HPV positivity and prevalence of CIN3+ in women with positive HPV varies considerably among studies and countries. These ranges impact the optimal Sn and Sp to generate optimal PPV and NPV. The NPV should be ≥96%. Countries with higher risk-aversion accept a lower PPV than countries that place more emphasis on avoiding unnecessary colposcopies (desirable levels range from ≥10% to ≥20%). Equivalence to cytology is lowest acceptable performance specification. Adding genotyping to any triage test improves Sn and usually decreases Sp. The minimal acceptable and target (optimal) performance specifications (Sn, Sp, PPV, NPV) are presented in tables and graphs.

Conclusions: The optimal performance specifications of a triage test for HPV-positive specimens will be superior to cytology and be equivalent or superior to newer technologies such as immunohistochemical staining and methylation. Different test clinical cutoffs may be desirable for different countries, and may need to change over time due to HPV vaccination effects. Self-sampling may drive interest in triage tests that do not require direct sampling of the transformation zone.

#2397

9 - HPV screening

MANAGEMENT OF HPV POSITIVE WOMEN IN CERVICAL CANCER SCREENING: RISK STRATIFICATION BY HPV GENOTYPE AND CYTOLOGY

Thomsen L[1], Kjaer S[2], Munk C[3], Oernskov D[4], Waldstroem M[5]

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

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

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

[4]LILLEBAELT HOSPITAL, Vejle, Denmark

[5]Department of Pathology, Vejle Hospital, Lillebælt Hospital, Region of Southern Denmark., Vejle, Denmark

Background/Objectives: Human papillomavirus (HPV)-based cervical cancer screening is implemented in an increasing number of countries, but the optimal management of high-risk (hr)HPV positive women remains uncertain. To inform management strategies for hrHPV positive women, we estimated the absolute risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in hrHPV positive women according to HPV type and cytological status in a Danish screening population.

Methods: We used data from a large Danish pilot implementation of HPV-based cervical cancer screening. During May 2017-October 2018, women aged 30-59 screened in the uptake area of the Department of Pathology, Vejle Hospital, Region of Southern Denmark, were screened by primary HPV testing or primary cytology depending on municipality of residence. In the HPV group, women were referred to immediate colposcopy if they had HPV16/18 (with any cytology), or 12 other hrHPV types and ≥ASCUS. We obtained information on screening results and subsequent histological diagnoses from a nationwide pathology register. Kaplan-Meier's method was used to estimate the absolute risk of CIN3+ at 12 months after referral, depending on HPV type (16/18 versus 12 other hrHPV) and cytology (normal, ASCUS/LSIL, ≥HSIL). We considered a CIN3+-risk of ≥10% as the acceptable risk threshold for referral (1).

Results: We included 1,433 hrHPV positive women, of whom 600 were referred to immediate colposcopy. In women with HPV16/18 (n=343), the risk of CIN3+ exceeded the colposcopy referral threshold, both among those with ≥HSIL (90.0%; 95% CI, 80.0%-95.9%), ASCUS/LSIL (26.2%; 95% CI, 17.1%-38.7%) and normal cytology (17.0%; 95% CI, 12.6%-22.7%). In women with non-16/18 hrHPV (n=257), those with ≥HSIL had high risk of CIN3+ (66.7%; 95% CI, 55.3%-77.7%), whereas the risk in those with ASCUS/LSIL was below the referral threshold (7.9%, 95% CI, 4.8%-12.7%).

Conclusions: Our findings support the utility of HPV genotyping for cervical cancer screening. The results indicate that women with non-16/18 hrHPV types and ASCUS/LSIL may safely be referred to 12-month early recall instead of immediate colposcopy, which could reduce immediate referrals by ≈30%. Updated results with a larger study population (~3,000 HPV positive women) and stratification by age will be presented.

References: (1) Arbyn M et al. Use of HC2 to triage women with borderline and mild dyskaryosis in the UK. Br J Cancer. 2011;105:877-80. PLEASE NOTE ADDITIONAL AFFILIATIONS FOR TWO CO-AUTHORS (additional affiliations could not be entered in the online system): KJÆR SK: Department of Gynecology, Rigshospitalet University Hospital, Copenhagen, Denmark. WALDSTRØM M: Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark.

#2344

22 - Diagnostic procedures / management

CLINICAL CHALLENGES IN MANAGING CERVICAL INTRAEPITHELIAL NEOPLASIA 2: REPORT FROM A CROSS-SECTIONAL SURVEY

Bradbury M[1], Centeno C[2], Pérez-benavente A[3], Gil-moreno A[4]

[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain

[2]Hospital Universitari Vall d'Hebron, Barcelona, Spain

[3]Hospital Universitari Vall d'Hebron, Barcelona, Spain

[4]Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background/Objectives: The management of CIN2 lesions remains controversial. Conservative management is now considered an acceptable approach in young women concerned about the adverse effects of treatment on future pregnancy outcomes. Despite the availability of consensus guidelines and recommendations for the management of CIN2, we are unaware of how colposcopists actually manage CIN2 lesions in routine clinical practice and their current views on the diagnosis of the disease. The aim of this nationwide survey was to determine the current management strategies offered to women with CIN2 lesions, to ascertain the attitude of colposcopists towards the histological diagnosis of CIN2 and to identify the criteria used to select women for conservative management

Methods: We conducted a cross-sectional nationwide survey among colposcopists working in Spain. Members of the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) and the Spanish Society of Gynecology and Obstetrics (SEGO) were invited to participate in an online questionnaire between the 12th June 2020 and the 21st July 2020. Only those members who were totally or partially dedicated to colposcopy were eligible to participate in the survey. The electronic questionnaire included 42 questions that covered the three main objectives of the study: how colposcopists manage women with CIN2, their opinion on the natural history and classification of CIN2 and their selection criteria for offering conservative management. All questionnaires were anonymous and participants' were offered the choice of including their work center at the end of the survey if they were willing to participate in a multicenter study assessing CIN2 management outcomes

Results: A total of 182 colposcopists, who were representative of all the autonomous regions in Spain, responded to the online survey. The median response rate was 95.7% (IQR 90.7 - 99.5%). Eighty-seven percent of respondents offer conservative management, with the majority offering observation in selected cases only (84.5%). The most common follow-up interval is 6 months (65%), followed by 3-4 months (30%). Conservative management is considered to be no longer appropriate after 24 motnths by 29.5% of respondents, 12 months by 26.3% and 24.3% expressed it depended on women' preference and plan to conceive. During conservative management, 93.9% always perform a cytology, 62.7% HPV testing, 96.8% colposcopy, 47.9% cervical biopsy and 28.1% endocervical curettage. Almost all respondents (92.9%) offer excisional treatment if CIN2 lesion persists. Fourty-five percent of respondents consider CIN2 merely represents a misclassified CIN1 or CIN3 and 46.2% believe CIN2 lesions are unlikely to spontaneously regress. When considering treatment of CIN2, 87.9% agree that a colposcopy-guided biopsy can sometimes act as a treatment and 66.7% believe delaying treatment of CIN2 can be cost-effective. Most respondents considered age >40 years (81.3%), HPV 16 infection (62.1%), HIV infection (76.8%), positive p16 immunostaining (60.2%), a large lesion occupying >50% of the cervix (87%), endocervical involvement (91.6%) and previous treatment for CIN2-3 (77%) are contraindications for conservative management

Conclusions: Management of CIN2 remains challenging for colposcopists and a lack of consensus still exists in clinical practice. A better understanding of the natural history of CIN2 and its clinical outcomes is still necessary in order to guide clinicians in its management

References: Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis. 2020;24(2):102-131. Tainio K, Athanasiou A, Tikkinen KAO, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: Systematic review and meta-analysis. BMJ. 2018;360. Silver MI, Gage JC, Schiffman M, et al. Clinical outcomes after conservative management of cervical intraepithelial neoplasia grade 2 (CIN2) in Women Ages 21-39 Years. Cancer Prev Res. 2018;11(3):165-170. Dempster-Rivett K, Innes CR, Simcock BJ, et al. Evaluation of guidelines for observational management of cervical intraepithelial neoplasia 2 in young women. Am J Obstet Gynecol. 2020 Sep;223(3):408.e1-408.e11

#2368

24 - Cervical neoplasia

ARE WOMEN AFTER SURGICAL TREATMENT OF HIGH GRADE CERVICAL INTRAEPITHELIAL LESIONS FOLLOWED-UP ACCORDING TO GUIDELINES?

Jančar N[1], Rajterič Brečko T[2], Ivanuš U[3]

[1]Division of obstetrics and gynecology, University Medical Centre Ljubljana, Slovenia, Ljubljana, Slovenia

[2]General hospital Novo mesto, Novo Mesto, Slovenia

[3]Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background/Objectives: Since organization and implementation of the national cervical screening program ZORA and the Guidelines for the comprehensive treatment of women with precancerous cervical changes in 2003, we have managed to halve the incidence of cervical cancer in Slovenia. This was achieved by implementing regular preventive check-ups, timely treatment of precancerous lesions and stringent post-procedure follow-up. The aim of this study was to determine whether women, who had a surgical treatment of high grade cervical intraepithelial lesions were followed-up according to the national guidelines.

Methods: We collected data from computer database of Patohistological laboratory of the Division of Obstetrics and Gynecology of the Ljubljana University Medical Centre and searched for patients who had surgical excision of cervical precancerous lesions (LLETZ or classical conisation) between January 1st 2014 and December 31th 2015. In addition, we collected histological reports of these excisions from hospital information system Hipokrat. A total of 842 women with histological diagnosis of high grade squamous intraepithelial lesion (HSIL) and cervical cancer was included. Relevant information on PAP smears, human papillomavirus (HPV) status and any additional procedures following primary excision procedure were provided by the National cervical cancer screening program and register ZORA. In the observation period, 4 years post procedure, we verified if all recommended PAP and HPV smears were performed. Using these data, we calculated the risk of HSIL or cancer in relation to the status of endocervical crypts and first PAP and HPV smear results after procedure. Data were presented using a survivorship curve.

Results: According to the status of surgical margin of conus women were arranged into two groups: the first group consisted of those who should have been followed up by PAP and HPV smears and the second group of those who should have had an immediate re-surgery. Only 28% (237/842) of women included were followed up according to the national guidelines. These women had all recommended smears within the 2.5 year period. Among women who were not managed according to the guidelines 3.6% never came for a planned visit, however, the majority of women had at least one PAP smear or combination of PAP and HPV smear. The highest risk for occurrence of HSIL+ 4 years after procedure was in the group of women with a massive invasion of dysplasia into endocervical crypts (15.2%), where the first PAP smear showed pathology (19.5% risk; in case of HSIL up to 65%) and when HPV smear was positive (24.2% risk).

Conclusions: Based on our research we can conclude that only 28% of women were followed-up appropriately; however, also the proportion of women who have never visited their gynecologist after procedure was relatively low (3.6%). We were also able to establish that women with a massive invasion into crypts, with HSIL in first PAP smear after procedure and a positive HPV smear after procedure are at greater risk for recurrence of the disease. During the 4-year post-procedure observation period all three criteria had similar predictors for recurrence. On the contrary, a negative HPV test result had the highest negative predictive value. Prevention strategies such as screening and vaccination against HPV, early recognition and treatment of precancerous lesions and close follow-up after procedure are crucial for maintaining low incidence of cervical cancer.

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#1395

7 - Immunotherapy - Immuno-oncology - New treatments

REAL-LIFE EFFICACY OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HIGH-RISK HPV PATIENTS: INTERIM ANALYSIS

Gaslain Y[1], Cortés J[2], De Santiago J[3], Sanjuán M[4], Agenjo M[5], Fiol G[6], Garcia C[7], Gurrea M[8], Hernández P[9], Dexeus D[10]

[1]Procare Health Iberia, , Spain

[2]Private Practice, , Spain

[3]Centro Oncológico MD Anderson, Madrid, Spain

[4]Clínica Ginemed, Sevilla, Spain

[5]Hospital Sanitas La Zarzuela, Madrid, Spain

[6]Private Practice, Almería, Spain

[7]Hospital HM San Francisco, , Spain

[8]Hospital La Fe , Valencia, Spain

[9]Private Practice, Oviedo, Spain

[10]WOMEN'S HEALTH INSTITUTE, , Spain

Background/Objectives: Real-life studies inform on the "effectiveness" of a treatment what is intended to do in routine circumstances. The aim of this study is to evaluate the efficacy of Papilocare® - a multi-ingredient Coriolus versicolor-based vaginal gel- on repairing high-risk (HR) HPV-dependent low-degree cervical lesions and HR-HPV clearance in real-life practice.

Methods: Observational, multicenter, prospective, one-cohort study (PAPILOBS study ClinicalTrial.gov: NCT04199260). Currently recruiting 300 vaccinated or not HPV-positive women aged > 25y with Pap smear of ASCUS or LSIL and concordant colposcopy during routine clinical visits in Spain. Patients are treated with Papilocare® 1 cannula/day for 21 days the first month + 1 cannula/alternate days for 5 months. After this 6-month period, patients with altered cytology and/or HPV persistency are treated for a 6-month extension treatment period with the same dosage. Interim analysis of HR-HPV patients with normal Pap smear and concordant colposcopy image (primary endpoint) and patient with HR-HPV cleared (patients with total clearance or partial clearance together with negative Pap smear and normal colposcopy) at 6/12 months is presented. The study was approved by the ethical committee of Public University Hospital of Puerta de Hierro (Madrid). Informed consent was signed by all patients.

Results: At 6 months, data of 148 and 146 patients for Pap smear/colposcopy and HR-HPV presence, respectively, were available. 67.6% of patients (100/148) had negative Pap smear and concordant colposcopy. HR-HPV clearance was observed in 58.9% of patients (86/146). Data of 46 and 44 patients included in the 6-month extension treatment period for Pap smear/colposcopy and HR-HPV presence, respectively, were available. At 12 months, 78.3% (36/46) of patients had negative Pap smear and concordant colposcopy and HR-HPV clearance was observed in 70.5% (31/44). Considering all study period, 77% (114/148) and 72.6% (106/146) of patients repaired HR-HPV-dependent cervical lesions and cleared HR-HPV, respectively.

Conclusions: In this interim analysis, repairing of HR-HPV-dependent low-degree cervical lesions and clearing HR-HPV, in real life conditions, was achieved after 6-month treatment with Papilocare® (or extending it up to 12-months if needed) in 3 out of 4 patients. These findings need to be confirmed upon study completion.

FC02 - HPV Testing / Molecular Markers I

#2254

12 - Molecular markers

CIRCULATING HPV DNA IN CERVICAL CANCER: A MARKER FOR EARLY DETECTION OF RELAPSE

Jeannot E[1], Latouche A[2], Bonneau C[3], Calméjane M[4], Beaufort C[5], Ruigrok-ritstier K[6], Bataillon G[7], Larbi Cherif L[8], Dupain C[9], Popovic M[10], De La Rochefordière A[11], Lecuru F[12], Fourchotte V[13], Jordanova E[14], Von Der Leyen H[15], Tran-perennou C[16], Legrier M[17], Dureau S[18], Raizonville L[19], Bello D[20], Le Tourneau C[21], Bièche I[22], Rouzier R[23], Berns E[24], Kamal M[25], Scholl S[26]

[1]INSTITUT CURIE, Paris, France

[2]Institut Curie, Saint-cloud, France

[3]Institut Curie, Saint-cloud, France

[4]Institut Curie, Paris, France

[5]Erasmus Medical Centre: Erasmus MC, Rotterdam, Netherlands

[6]Erasmus Medical Centre: Erasmus MC, Rotterdam, Netherlands

[7]Institut Curie, Paris, France

[8]INSTITUT CURIE, Paris, France

[9]Institut Curie, Paris, France

[10]Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

[11]Institut Curie, Paris, France

[12]Institut Curie, Paris, France

[13]Institut Curie, Paris, France

[14]Netherlands Cancer Institute: Antoni van Leeuwenhoek Nederlands Kanker Instituut, Amsterdam, Netherlands

[15]Hannover Medical School: Medizinische Hochschule Hannover, Hannover, Germany

[16]Institut Curie, Paris, France

[17]Institut Curie, Saint-cloud, France

[18]Institut Curie, Saint-cloud, France

[19]Institut Curie, Saint-cloud, France

[20]Institut Curie, Saint-cloud, France

[21]Institut Curie, Saint-cloud, France

[22]Institut Curie, Paris, France

[23]Institut Curie, Saint-cloud, France

[24]Erasmus Medical Centre: Erasmus MC, Rotterdam, Netherlands

[25]Institut Curie, Paris, France

[26]Institut Curie, Paris, France

Background/Objectives: Almost all cervical cancers (CC) are caused by human papillomavirus (HPV) and patients with advanced stage are at high risk for relapse. Circulating HPV DNA (HPV ctDNA) may serve as a residual tumor marker at the end of chemo-radiation or to predict relapse during the follow-up period.

Methods: We analyzed serum samples from 94 HPV16- or HPV18-related CCs from the BioRAIDs prospective cohort. Samples were collected before and after treatment and during an 18-month follow-up period. Using digital droplet PCR (ddPCR), we assessed the relevance of circulating HPV E7 gene as a marker for residual disease compared to HPV integration site and PIK3CA mutations. Finally, the prognostic impact of circulating HPV E7 gene was assessed with its prediction value of relapse.

Results: HPV E7 gene was the most sensitive tumor marker, superior to both HPV integration sites and PIK3CA mutations in serum. Circulating HPV DNA (HPV ctDNA) was detected in 63% (59/94) of patients, before treatment. HPV ctDNA detection in serum sample was associated with high FIGO stage (p=0.02) and para-aortic lymph node involvement (p=0.01). The level of HPV ctDNA was positively correlated with HPV copy number in the tumor (R=0.39, p<0.001). Complete clearance of HPV ctDNA by the end of treatment was significantly associated with a longer PFS (p<0.0001). Patients with persistent HPV ctDNA in serum relapsed with a median time of 10 months (range, 2-15) from HPV ctDNA detection.

Conclusions: HPV ctDNA detection is a useful marker to predict relapse in CC.

#2282

20 - New technologies

MULTIPLEXED QUANTIFICATION OF BIOMARKERS DETECTS DYSPLASIA WITH HIGH ACCURARCY: A VALIDATION OF THE QG-MPH USING RT-QPCR

Skof A[1], Nevermann N[2], Basten M[3], Choli N[4], Boschetti Grützmacher E[5], Sehouli J[6], Kaufmann A[7]

[1]CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

[2]Charité - Clinic for gynaecology, Berlin, Germany

[3]Charité - Clinic for gynaecology, Berlin, Germany

[4]Institut für Zytologie und Dysplasie, Fürstenbergkarree , Berlin, Germany

[5]Charité - Clinic for gynaecology, Berlin, Germany

[6]Charité - Clinic for gynaecology, Berlin, Germany

[7]CLINIC FOR GYNECOLOGY, CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

Background/Objectives: Cervical cancer is caused by persistent HPV infection and is characterized by a pre-malignant continuum of dysplastic changes ranging from CIN I to CIN III. During the progression to cervical cancer, the expression of HPV oncogenes and cellular biomarkers is upregulated. Qualitative detection and quantification of the strength of these markers could be used to discriminate the different clinical stages and could help triaging women screened positive in cytology- or HPV-based screening.

Methods: We used the Luminex bead-based QuantiGene 2.0 technology platform (Thermo Fisher Scientific) to detect and quantify simultaneously the mRNA expression of HPV genotype-specific oncogenes as well as cellular biomarkers from a crude lysate of a cervical smear sample. Biomarkers include for example proliferation markers, tumor stem cell markers, and tumor markers. To validate the data from the QuantiGene-molecular-histology-assay (QG-MPH) we performed RT-qPCR analysis for a representative set of cervical samples and the most informative biomarkers: HPV16-E7, HPV18-E7, STMN1, BIRC5, MCM2, Ki67, ALDH1A1, CDKN2A, TERT, UBC, and ACTB. We used Spearman rank correlation to compare the QG-MPH with the RT-qPCR Data, as well as the marker expression with the clinical stages. ROC analysis was also performed for both methods, marker-sets, and Risc-Scores for the clinical borders CIN2+, CIN3+ and CxCa were developed.

Results: QG-MPH distinguishes the clinical stages with high accuracy. ROC analysis showed an AUC of 0.808 with a sensitivity of 82.5% and specificity of 63.3% for the detection of CIN3 or higher (n=1135). Comparing the RT-qPCR data with the QG-MPH data, correlation coefficients between -0.33 and -0.9 (rs) for the different markers were observed. The ROC analysis of the RT-qPCR showed a similar AUC with 0.83 and a sensitivity of 76% and a specificity of 85% for the detection of CIN3+ (representative subset n=74). Comparable results were found for the clinical borders CIN2+ and CxCa. Comparing the hands-on-time and costs between both methods, QG-MPH is the quicker (2h vs. 9 h 15 min for 40-plex) and cheaper (0.49€ vs. 2.39€ per data point) method. Because of the obsolete RNA extraction step QG-MPH is also more robust and with a lower contamination risk.

Conclusions: The mRNA quantification by QuantiGene Plex is reliable and reproducible by RT-qPCR. Both methods distinguish the clinical stages with high accuracy. mRNA quantification with QG-MPH is technically simple and more robust than RT-qPCR and may be used as a triage method after primary HPV-testing also in LMIC settings to avoid over referral.

#1852

26 - Vulvar diseases and neoplasia

Evaluation of dyskerin expression and the Cajal body protein WRAP53ß as potential prognostic markers for patients with primary vaginal carcinoma

Ranhem C[1], Larsson G[2], Farnebo M[3], Kashuba E[4], Andersson S[5]

[1]KAROLINSKA INSTITUTET, Västerås, Sweden

[2]Orebro University Hospital, örebro, Sweden

[3]Karolinska Institutet, Stockholm, Sweden

[4]Karolinska Institutet, Stockholm, Sweden

[5]Karolinska Institutet, Stockholm, Sweden

Background/Objectives: Primary vaginal cancer (PVC) is a rare gynecological malignancy without appropriate biomarkers for prognosis. The majority of the cases are HPV related and most commonly affects postmenopausal women. it is mainly treated with radiation therapy, with or without concurrent chemotherapy, resulting in cancer-specific 5-year survival rates of about 70%. Identification of new biomarkers is essential to improve diagnosis, treatment outcome and prognosis for patients with PVC. Dyskerin and WRAP53ß, which both exert their functions in the telomerase holoenzyme complex, involved in modification of nuclear RNAs and telomere elongation, have previously been shown to be overexpressed and of prognostic significance in different cancers. The aim of this study was to examine the expression patterns of WRAP53ß and dyskerin in PVC. Moreover, we wanted to evaluate possible associations of expression of these two proteins with clinical characteristics and survival in our search for potential prognostic biomarkers for PVC.

Methods: This retrospective study, based on archived diagnostic PVC tumor tissue samples, includes a consecutive cohort of 81 patients with PVC diagnosed and treated between 1975 and 2002 at Örebro University Hospital, as well as at the central hospitals in Eskilstuna, Västerås, and Karlstad, Sweden. PVC tumour samples from 68 patients diagnosed with PVC were immunohistochemically evaluated for the expression of dyskerin and WRAP53ß. The results were evaluated for associations with clinical variables and survival.

Results: The majority of tumour samples showed low expression of dyskerin. A significant association was shown between dyskerin expression and clinical findings, including histological type and to tumour differentiation. It was also associated to variables of cancer progression and to poor prognosis. Patients with tumors characterized by high dyskerin expression had a significantly lower 5-year cancer-specific survival rate (log-rank test; $p = 0.009$). Dyskerin expression was found to be a significant independent prognostic factor (Cox multivariate proportional regression analysis: $p = 0.032$). WRAP53ß was also expressed in the majority of cells but was not significantly associated with clinical variables or survival.

Conclusions: This study demonstrates that overexpression of dyskerin significantly correlates with poor prognosis, and dyskerin may serve as a promising prognostic marker and a potential putative therapeutic target in PVC.

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#2308

20 - New technologies

QUANTIGENE-MOLECULAR PROFILING HISTOLOGY ASSAY DETECTS DYSPLASIA FROM PRIMARY CERVICAL SMEAR SAMPLES WITH HIGH PRECISION BY MULTIPLEXED MRNA QUANTITATION OF BIOMARKERS

Skof A[1], Schreckenberger C[2], Nevermann N[3], Basten M[4], Schneider A[5], Grützmacher Boschetti E[6], Sehouli J[7], Kaufmann A[8]

[1]CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

[2]CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, , Germany

[3]Clinic for Gynecology, Charité-Universitaetsmedizin Berlin, Berlin, Germany

[4]Clinic for Gynecology, Charité-Universitaetsmedizin Berlin, Berlin, Germany

[5]Institut für Zytologie und Dysplasie,MVZ im Fürstenbergkarree Berlin, Berlin, Germany

[6]Clinic for Gynecology, Charité-Universitaetsmedizin Berlin, Berlin, Germany

[7]Clinic for Gynecology, Charité-Universitaetsmedizin Berlin, Berlin, Germany

[8]CLINIC FOR GYNECOLOGY, CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

Background/Objectives: Persistent infection by Human Papillomaviruses (HPV) is characterized by viral oncogene E6/E7 expression and upregulation of cellular proteins used as biomarkers for infection and transformation. E6 and E7 have pleiotropic effects and interact with several cellular proteins regulating proliferation, tumor suppressors, (cancer) stem cell markers, and tumor markers. The strength of oncogene and biomarker expression correlates to dysplasia size, stage and progression potential. The objective of this method development was to achieve a comprehensive and informative diagnostic result by evaluating the biomarker expression pattern and strength.

Methods: We developed a multiplexed mRNA quantifying assay based on Luminex/QuantiGene 2.0 technology platform (Thermo Fisher Scientific) termed QuantiGene-Molecular-Profiling-Histology (QG-MPH). It combines detection of the E7 mRNA of 18 high-risk HPV genotypes and 18 cellular biomarkers, routinely used for diagnosis, markers for cancer stem cells, tumor markers and housekeeping genes for normalization. All mRNA species are detected and quantitated simultaneously from a crude lysate of a cervical smear sample taken into Thinprep/PreserveCyte. In a prospective trial 1400 consecutively collected samples were measured and data used for logistic regression and ROC analyses to identify the most informative marker combinations for different dysplastic stages.

Results: The QG-MPH assay has a high sensitivity detecting less than 40 CaSki or HeLa cells. It genotypes 18 HR-HPVs and identifies leading types in multiple infections by their strongest E7 expression. Logistic regression identified E7 expression strength as most informative biomarker discriminating low grade and high grade (CIN2+) dysplasia. P16, proliferation associated markers (Ki67, MCM2, Stathmin), and tumor markers (ALDH1A1, BIRC5, hTERT) contributed to detection and differentiation of dysplastic stages. Risc score formulas were developed for discrimination of CIN2+ and CIN3+ and invasive cervical cancer. Accuracy by ROC analysis to detect CIN3+ from the initial screening sample was 90%.

Conclusions: mRNA quantification of viral and cellular biomarkers by QuantiGene 2.0 Plex assay detects HPV infection and dysplasia with high accuracy. The assay could be used as a triage to colposcopy after primary HPV screening. QG-MPH assay procedure is simple and robust and due to multiplexing cost effective. It may accelerate screening, triage, and diagnosis and maybe used in LMIC settings to reduce further triage and avoid overreferral.

#2178

20 - New technologies

Circulating HPV DNA as a biomarker in patients with HPV related cervical carcinoma

Bryan S[1], Lee J[2], Gunu R[3], Jones A[4], Olaitan A[5], Rosenthal A[6], Bhide S[7]

[1]UNIVERSITY COLLEGE LONDON, Essex, United Kingdom
[2]The Institute of Cancer Research, London, United Kingdom
[3]University College London, London, United Kingdom
[4]University College London, London, United Kingdom
[5]University College London Hospital, London, United Kingdom
[6]University College London, London, United Kingdom
[7]The Institute of Cancer Research, London, United Kingdom

Background/Objectives: High risk HPV infection is responsible for >99% of cervix cancers. HPV utilises mucosal breaks to enter epithelial cells and integrate with the host genome, causing viral infection and replication. In persistent infections that lead to cancer, the tumour breaches the basement membrane releasing HPV DNA into the bloodstream. A next generation sequencing assay (NGS) for detection of plasma HPV circulating DNA (HPV cDNA) for high-risk HPV sub-types, 16, 18, 31, 33, 35, 45, 52, and 58 has been developed and demonstrates 88% sensitivity and 100% specificity in patients with locally advanced cervix cancers undergoing radical chemoradiation (manuscript in preparation). We investigated this expanded panel assay in pre-invasive and invasive cervical lesions, testing the hypothesis that HPV cDNA is detectable in invasive cancers but not pre-invasive lesions.

Methods: We recruited two cohorts of patients: those undergoing excisional treatment of high-grade cervical intra-epithelial neoplasia (CIN) and those with biopsy-confirmed early invasive carcinoma of the cervix (1A-1B). After gaining informed consent, a blood sample was taken from these patients immediately prior to treatment and again at their follow-up appointment. DNA extraction from plasma followed by NGS were used for detection of HPV cDNA.

Results: We recruited 52 patients, 40 (77%) with high grade lesions and 12 (23%) with early invasive tumours. None of the patients had prior HPV vaccination. Adequate DNA for sequencing was extracted from 50 (96%) baseline samples. None of the patients with high grade, pre-invasive lesions were positive for HPV cDNA. Two of the samples from the invasive cancers were found to be > stage 1B at follow up and therefore excluded from the results. Of the remaining 10 invasive tumours, 1 (10%) reached the threshold of positivity for HPV cDNA in plasma; detecting subtype 18 which correlated with the HPV type at referral. Re-calculating the thresholds for positivity did not increase the detection of HPV cDNA in plasma in early stage (<=1B) tumours.

Conclusions: We have confirmed that HPV cDNA is absent in high grade CIN. In early cervical tumours, there was very low detection of HPV cDNA. This may be explained by small tumour size, with poorer access to lymphatics and the circulation, compared with higher stage tumours, and therefore little shedding of HPV cDNA in plasma at detectable levels. The detection rate of HPV cDNA in patients with early invasive carcinoma of cervix (IA-IB) using even the most sensitive of currently available technologies i.e., NGS is sub optimal. More sensitive assays are required before HPV cDNA can be used as a biomarker in this setting.

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FC03 - Screening I

#2312

14 - Screening methods

EFFECTS OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER IN GERMANY: RESULTS FROM A POPULATION-BASED CASE-CONTROL STUDY

Tanaka L[1], Schriefer D[2], Schauberger G[3], Klug S[4]

[1]TUM, Munich, Germany

[2]TUD, Dresden, Germany

[3]TUM, Munich, Germany

[4]TUM, Munich, Germany

Background/Objectives: Despite the existence of an opportunistic cervical cancer screening in Germany since 1971, the incidence of cervical cancer in Germany remains relatively high in comparison with other western European countries. Within a population-based case-control study, we investigated the impact of opportunistic cervical cancer screening on cervical cancer in Germany.

Methods: We recruited incident cases of cervical cancer (ICD-10 C53) from Saxony, Rhineland-Palatinate, and neighbouring regions, diagnosed between 2012 and 2016 and matched with three population-based controls, based on age and region of residence. In a structured telephone interview, study participants reported their frequency of cervical cancer screening participation in the past ten years and other relevant variables. We fitted conditional logistic regression models and reported odds ratios (OR) and 95% confidence intervals (95% CI) by histologic group (squamous cell and adenocarcinoma), T category (T1 and T2+), and age (<50 and ≥50 years).

Results: We included 217 cases and 652 matched controls in our analyses. About 50% of cases and 85% of controls attended cervical cancer screening frequently. Among cases with T1 and T2+ tumours, frequent cervical cancer screening attendance was around 60% and 25%, respectively. After adjusting for significant variables, frequent participation in cervical cancer screening reduced the risk of cervical cancer by about 80% (approximately 85% for squamous cell and 75% for adenocarcinoma). The reduction was 90% for larger tumours (T2+).

Conclusions: Although opportunistic cervical cancer screening Germany significantly reduced the risk of cervical cancer, especially larger tumours, the high proportion of cases who had been screened at least once in the three years prior to diagnosis underscores the need to investigate the quality of cytology and treatment of precancerous lesions in Germany.

#2205

38 - Public health

SCREENING PARTICIPATION AFTER A FALSE POSITIVE SCREENING RESULT

Larsen P[1], Njor S[2]

[1]Randers Regional Hospital, Randers Nø, Denmark

[2]Randers Regional Hospital, Randers, Denmark

Background/Objectives: As number of false positive tests are expected to increase with the introduction of human papillomavirus (HPV) based cervical cancer screening (1), it is important to know if receiving a false positive test affects subsequent cervical cancer screening participation, as this will then reduce the preventive effect of HPV based cervical cancer screening.

Methods: This Danish nationwide register-based cohort study included 502,380 women aged 22.5-45 attending cervical cancer screening in 2012-2014 with a normal (n=501,003) or FP (n=1,377) cytology screening result. A FP result was defined as a cervical cytology showing high grade cytological abnormalities followed by a normal or "Cervical Intraepithelial Neoplasia grade 1' biopsy result. Women were categorized as subsequent participants if they had a cervical cytology within 24 to 42 months after their last screening or surveillance test. We compared subsequent participation among women with a normal versus a FP result, using odds ratios including 95% confidence intervals.

Results: Participation was slightly higher among women with FP results than among women with normal results (71.5% vs. 69.2 %, p=0.058). After adjustment for age and screening history, women with FP results participated significantly more than women with normal results (OR: 1.19, 95% CI: 1.06 - 1.35).

Conclusions: As HPV testing is more sensitive at detecting CIN2+, but less specific than cytology-based screening, the proportion of false positive results is expected to increase (1). Our study shows that this will probably not affect screening participation and thereby not lower the effect of the screening programs. However, our study only included women below 45 years wherefore it is unknown if older women receiving a false positive result will also not have a reduced participation rate in subsequent cervical cancer screening.

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#2277

9 - HPV screening

HPV is looking around the corner, beware of your anus when you screen the cervix

Pache B[1], Vincent B[2], Mathis J[3], Hübner M[4], Mathevet P[5], Jacot-guillarmod M[6]

[1]1. Gynaecology Department, Centre Hospitalier Universitaire Vaudois CHUV, Lausanne, Switzerland

[2]1. Gynaecology Department, Centre Hospitalier Universitaire Vaudois CHUV, Lausanne, Switzerland

[3]1. Gynaecology Department, Hopital de Bienne, Bienne, Switzerland

[4]2. Visceral surgery Department, Centre Hospitalier Universitaire Vaudois CHUV, Lausanne, Switzerland

[5]1. Gynaecology Department, Centre Hospitalier Universitaire Vaudois CHUV, Lausanne, Switzerland

[6]1. Gynaecology Department, Centre Hospitalier Universitaire Vaudois CHUV, Lausanne, Switzerland

Background/Objectives: Human Papillomavirus (HPV) is a highly prevalent virus in sexually active population and carries a significant burden in all class ages. High risk (HR) genotypes of HPV are linked to risks of dysplasia and cancers. The natural history of HPV on cervix is well known. On the other hand, anal HPV-induced cancer is increasing in women. Currently, there is no evidence-based data of the correlation between cervical and anal HR-HPV. The objective was to identify risk factors for cervical HPV, and the concomitant presence of anal HPV in patients with cervical HR-HPV.

Methods: Prospective cohort of women recruited in a tertiary university hospital in Switzerland. Cervical and anal screening of HPV genotyping and cytology were performed. Statistical analysis was performed with Chi2 for qualitative data and t-test for quantitative data.

Results: Overall, 274 patients were analyzed. Mean age was 42+/- 12 years. 102 women (37%) had HR-HPV. They were significantly younger (39 vs 44 yrs, p<0.001), had sex earlier (17,2 vs 18,3 yrs, p<0.01), have had more sexual partner (2,9 vs 2,2, p<0.0001), had more cervical LR-HPV (38% vs 10%, p<0.0001) and more abnormal cervical cytologies (42% vs 19%, p<0.0001), had more anal LR-HPV (41% vs 26%, p:0.014) and HR-HPV (59% vs 24%, p<0.0001). On clinical examination, they had more abnormal cervix visual examination (54% vs 22%, p<0.0001). On anamnesis, they were more likely to use a contraception method (37% vs 24%, p:0.022), to have ever had anal intercourse (44% vs 29%, p:0.015), to have more gestity and parity, and to smoke (36%vs 15%, p<0.0001). Multivariate analysis retained anal HR-HPV as independent risk factor for cervical HR-HPV (OR 3.3, CI 1.2-9.0, p=0.02).

Conclusions: The results of this cohort shows that it is of upmost importance to screen women for anal HPV when cervical HR-HPV is found.

#1916

37 - Low resource settings

LESSONS FROM HPV SCREENING IMPLEMENTATION WITHIN PRIMARY CARE IN BURKINA FASO

Mensah K[1], Kaboré C[2], Zeba S[3], Bouchon M[4], Duchesne V[5], Pourette D[6], Debeaudrap P[7], Dumont A[8]

[1]Centre Population et Développement (CEPED), IRD, UP, Paris, France

[2]Institut de recherche en sciences de la santé (IRSS), Ouagadougou, Burkina Faso

[3]Laboratoire de Recherche Interdisciplinaire en Sciences sociales et Santé (LARISS), Université Ouaga 1, Ouagadougou, Burkina Faso

[4]Pôle Recherche et apprentissages, Médecins du Monde, Paris, France

[5]Centre Population et Développement (CEPED), IRD, UP, Paris, France

[6]Centre Population et Développement (CEPED), IRD, UP, Paris, France

[7]Centre Population et Développement (CEPED), IRD, UP, Paris, France

[8]Centre Population et Développement (CEPED), IRD, UP, Paris, France

Background/Objectives: Cervical cancer screening in sub-Saharan countries relies on primary visual inspection with acetic acid (VIA) with mixed success. While HPV-based screening is considered a promising alternative, its implementation in low-resource settings on a large scale will face human and structural challenges. The factors that could foster or hinder the implementation of this screening strategy and affect its real-life effectiveness remain under explored. In Ouagadougou, Burkina Faso, free HPV-based screening was implemented in 2019 in two primary healthcare centers. We carried out a process and effectiveness evaluation of this intervention.

Methods: We used a hybrid effectiveness-implementation type III mixed-methods study design. Effectiveness outcomes and implementation indicators were assessed through a cohort study of screened women, observations in participating centers, individual interviews with women and healthcare providers and monitoring reports. Screening completeness and women's satisfaction were the main effectiveness outcomes. We used logistic regression models and concurrent qualitative analysis to understand how implementation variability and acceptability by women and healthcare providers affected effectiveness outcomes.

Results: After a 3-month implementation period, of the 350 women included in the cohort, 94% completed the screening. Only 26% had their screening completed in a single visit as planned in the intervention. Although not planned, this multiple-visit adaptation emerged to meet the caregivers' workload constraints. The proportion of highly satisfied women was greater after result disclosure (95%) than after sampling (65%). A good understanding of screening results and recommendations increased screening completeness and women's satisfaction, while time to result disclosure decreased satisfaction. In addition, having a screening dedicated midwife was positively associated with women's satisfaction.

Conclusions: Free HPV-based screening was successfully integrated within primary care in Ouagadougou, Burkina Faso leading to a high level of screening completeness despite the frequent use of multiple visits. To be successful, large scale implementation of HPV-screening at primary level will need good quality counseling and reduced waiting times at the various steps of the screening sequence. These results provide significant insights for future implementation project in similar contexts.

#2371

9 - HPV screening

HPV SCREENING: PRACTICAL REALIZATION OF WHO GLOBAL STRATEGY ON CERVICAL CANCER ELIMINATION IN RUSSIA

Olkov I[1]

[1]SOCIAL PROGRAMS DEVELOPMENT FOUNDATION, Moscow, Russia

Background/Objectives: On 17.11.20 WHO officially announced the launch of a global strategy on elimination of cervical cancer. Among the keystones of this global strategy are a vision of a world where cervical cancer is eliminated as a public health problem, a threshold of 4 per 100k women and the meeting of 90-70-90 targets by 2030. The 70% principle stands for screening of the corresponding percentage of women with an HPV test by 35-45 years of age. HPV screening programs have already been initiated in Russian regions of Bashkortostan, Kaliningrad and Mordovia. More than 373 women a year develop cervical cancer and about 46% of these women die in the Republic of Bashkortostan. A cohort of 30.000 women at 30-39 years old, the group with the highest mortality rate, have been chosen for a local pilot HPV screening program.

Methods: Samples were simultaneously collected for HPV and conventional cytology (PAP). Women, positive by High-Risk HPV (hrHPV+) were triaged by PAP. HC2 technique (QIAGEN GmbH) was used for HPV testing. PAP results classified as ASC-US or more severe were considered abnormal. Colposcopy-directed biopsies of suspicious parts of the cervix were taken for histological examination from hrHPV+/PAP+ women referred for colposcopy. Histological results were classified as normal, CIN grades 1-2 -3, cancer in situ or invasive cancer.

Results: 30.000 women from 30 to 39 years were enrolled into the screening program and 29.052 (98,68%) were tested. 89,6% of the tested women had an adequate hrHPV test (n=26.023) while 10,4% (n= 3.029) appeared to be hrHPV+. HrHPV-negative women were excluded from the screening for the next 5 years interval. HrHPV+ but PAP negative women were advised for a follow-up testing in 12 months. 2.711 (89,5%) hrHPV+ and PAP+ women were referred for colposcopy. In this group 32,7% were diagnosed with various CIN grades (n=57) and 12,1% (n=21) with cancer in situ and invasive cancer. All these women have been duly treated.

Conclusions: HPV-testing appeared to be more sensitive for the detection of cervical precancer and cancer than cytology and proved to be a highly reliable technology for cervical cancer prevention. Cumulative costs for implementation of HPV screening were 1,5 times higher, while clinical efficiency appeared to be 2,5 times higher than PAP. We experienced difficulties in the reaching of women invited for screening. To overcome this, a complex informational and educational campaign was carried out for local gynaecologists and local women with the aid of Federal medical experts, volunteers and mass media. Two regional TV channels and more than 50 bloggers have been involved in the campaign.

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HN03 - Submitted Papers I

#1388

29 - HPV and oropharynx / Head and neck cancer

Survival of patients with oropharyngeal squamous cell carcinomas (OPSCC) in relation to TNM 8 - Risk of incorrect downstaging of HPV-mediated non-tonsillar, non-base of tongue carcinomas.

Marklund L[1], Holzhauser S[2], De Flon C[3], Zupancic M[4], Landin D[5], Kolev A[6], Haeggblom L[7], Munck-wikland E[8], Hammarstedt-nordenvall L[9], Dalianis T[10], Näsman A[11]

[1]KAROLINSKA UNIVERSITY HOSPITAL, Stockholm, Sweden

[2]KAROLINSKA INSTITUTET, Stockholm, Sweden

[3]Karolinska institutet, Stockholm, Sweden

[4]KAROLINSKA UNIVERSITY HOSPITAL, Bromma, Sweden

[5]KAROLINSKA UNIVERSITY HOSPITAL, Stockholm, Sweden

[6]Karolinska institutet, Stockholm, Sweden

[7]Karolinska institutet, Stockholm, Sweden

[8]Karolinska institutet, Stockholm, Sweden

[9]Karolinska institutet, Stockholm, Sweden

[10]KAROLINSKA INSTITUTE, Stockholm, Sweden

[11]KAROLINSKA INSTITUTET, Stockholm, Sweden

Background/Objectives: TNM-8 staging separates oropharyngeal squamous cell carcinomas (OPSCC) into human papillomavirus (HPV)-mediated and -unrelated OPSCC based on p16INK4a overexpression (p16+), as surrogate marker for HPV. However, OPSCC is histologically and clinically heterogenous including tonsillar and base of tongue squamous cell carcinomas (TSCC and BOTSCC respectively), and carcinomas of soft palate and walls (otherOPSCC). The significance of HPV is established in TSCC/BOTSCC, while its role in otherOPSCC is unclear, which is not considered in TNM-8. Here, p16+ was therefore evaluated in relation to overall survival (OS) and tumor stage per OPSCC subsite.

Methods: All 932 patients, treated with curative intent in Stockholm 2000-2016 with OPSCC, previously analyzed for p16 expression, were included. Clinical data, including stage and OS, was collected retrospectively.

Results: Patients with p16+ otherOPSCC had significantly poorer OS compared to patients with p16+ TSCC/BOTSCC (p=0.005) and their survival was similar to that of patients with p16- otherOPSCC/TSCC/BOTSCC. Moreover, patients with TNM-8 stage I-II and p16+ otherOPSCC had a significant poorer OS compared to patients with p16+ TSCC/BOTSCC and similar stage (p=0.02). Lastly, patients with otherOPSCC and low TNM-7 stage had a significant better OS, as compared to those with a high stage (p=0.019) while no hazard discrimination was observed with TNM-7 in TSCC/BOTSCC.

Conclusions: Our results indicate a risk of misclassification of patients with otherOPSCC and low TNM-8 stage. We suggest that p16 should only be evaluated in TSCC/BOTSCC and that patients with otherOPSCC should all be staged as patients with HPV-unrelated (p16-) OPSCC.

#1926

29 - HPV and oropharynx / Head and neck cancer

Patient derived ex vivo slice cultures demonstrate a profound DNA double-strand break repair defect in HPV-positive OPSCC

Zech H[1], Betz C[2], Kriegs M[3], Mansour W[4], Berger J[5], Busch C[6], Petersen C[7], Rothkamm K[8], Köcher S[9], Rieckmann T[10]

[1]Department of Otorhinolaryngology; University Medical Center Hamburg Eppendorf, Germany University Medical Center Hamburg Eppend, Hamburg , Germany

[2]Department of Otorhinolaryngology; University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[3]Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[4]Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[5]UNIVERSITY MEDICAL CENTER HAMBURG EPPENDORF, , Germany

[6]Department of Otorhinolaryngology; University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[7]Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[8]Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg Eppendorf, Germany , Hamburg, Germany

[9]DEPARTMENT OF RADIOTHERAPY AND RADIATION ONCOLOGY, UNIVERSITY MEDICAL CENTER HAMBURG EPPENDORF, , Germany

[10]UNIVERSITY MEDICAL CENTER HAMBURG-EPPENDORF, Hamburg, Germany

Background/Objectives: HPV-induced head and neck squamous cell carcinoma (HNSCC), which are mostly derived from the oropharynx, are more sensitive towards radiation than HPV-negative HNSCC. Two main theories exist regarding the underlying mechanism. While analyses of tumor tissues demonstrated stronger lymphocyte infiltration pointing to an enhanced immunogenicity, data from HPV-positive HNSCC cell lines suggest an enhanced cellular radiosensitivity based on a defect in DNA double-strand break (DSB) repair. The main limitation of the latter theory is that it has never been tested outside of HPV-positive HNSCC cell lines.

Methods: Human oropharyngeal SCC (OPSCC) samples, collected during surgery or panendoscopy, were cultivated ex vivo as 400 µm thick tumor slices. Slices were irradiated and after 24 h fixed and frozen. DSB repair capacity was assessed by immunofluorescence staining and subsequent quantification of residual 53BP1 nuclear foci in p63-positive tumor cells in cryosections. Samples with sufficient material were additionally treated with an inhibitor of the central DNA damage response kinase, ATM, before irradiation.

Results: OPSCC tissue slices proved suitable for ex vivo cultivation. Tumor cells in HPV-positive cultures (n=8) showed profoundly higher numbers of residual DSBs at 24 h after 3 Gy irradiation as compared to their HPV-negative counterparts (n=8), with on average 0.9 vs. 5.7 residual foci per nucleus, respectively (p=0.0003). Foci numbers after a higher dose of 6 Gy confirmed the difference in DSB repair (p=0.0010). As expected, ATM inhibition resulted in a severe increase in residual radiation induced foci in all HPV-negative samples tested (average increase: 4-fold; n=4) and also in the only HPV-positive sample that had demonstrated effective DSB repair. In contrast, ATM inhibition failed to increase residual foci numbers in all HPV-positive samples tested, that had demonstrated an impaired DSB repair capacity (n=6).

Conclusions: Our ex vivo data for the first time present robust evidence for a profound DSB repair defect of HPV-positive OPSCC in primary human tumor samples, fully supporting previous findings derived from established cell lines. The lack of effectiveness of ATM inhibition suggests an intrinsic defect regarding the ATM-orchestrated DNA damage response. Low numbers of residual 53BP1 foci in ex vivo irradiated HPV-positive samples may identify a minority of such patients with effective DSB repair, which are likely to be at higher risk for treatment failure and may have to be excluded from deintensification approaches.

#1387

29 - HPV and oropharynx / Head and neck cancer

Epidemiologic and survival distinctions between base of tongue and tonsil oropharyngeal carcinomas

Windon M[1], Fakhry C[2], Margalit D[3], Dey T[4], Rettig E[5]

[1]Johns Hopkins Hospital, Baltimore, United States

[2]Johns Hopkins Hospital, Baltimore, United States

[3]Dana-Farber Cancer Institute, Boston, United States

[4]Brigham and Women's Hospital, Boston, United States

[5]Brigham and Women's Hospital, Boston, United States

Background/Objectives: Human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPC) arises primarily from the lymphoid base of tongue (BOT) and palatine tonsillar tissues. To date these two anatomic subsites have been considered as one entity, however there may be important subsite-related differences. Our objective is to describe epidemiologic trends, tumor characteristics, and survival of HPV-positive BOT and tonsil tumors.

Methods: This is a retrospective cohort study of OPC cases included from 2004-2016 in the National Cancer Database (NCDB), and adults interviewed in the National Health and Nutrition Examination Survey (NHANES) 2011-2014. Demographic and tumor characteristics among OPC cases were compared by subsite. The association of subsite with overall survival (OS) for HPV-positive OPCs was examined using the Kaplan-Meier method and Cox Proportional Hazards modeling. Associations of demographic factors with self-reported history of tonsillectomy among NHANES participants were assessed using population-weighted logistic regression.

Results: HPV-positive BOT patients (N=13,081, 44%) were older than HPV-positive tonsil patients (N=16,874, 56%; mean 61.5 versus 58.4 years, $p<0.001$), and individuals 70+ years were significantly more likely to have BOT tumors compared with individuals <50 years old (adjusted odd ratio [aOR]=2.9, 95%CI=2.6-3.2). BOT patients were also more likely to be white (aOR=1.2, 95%CI=1.1-1.4), male (aOR=1.2, 95%CI=1.1-1.4), and have advanced tumor stage ($p_{trend}<0.001$). AJCC 7th Edition N0 BOT tumors had significantly worse survival than N0 tonsil tumors (adjusted HR [aHR] 1.28, 95%CI=1.03-1.56), and than N1 BOT tumors (aHR 0.73, 95%CI=0.59-0.91) (Figure 1). This unexpectedly reduced survival among N0 BOT compared with tonsil tumors was most pronounced among individuals 70+ years and those receiving trimodality therapy. Among 7,418 NHANES participants, self-reported history of tonsillectomy was associated with older age (aOR=3.6, 95%CI=3.0-4.2 for 70+ versus 40-49 year olds; $p_{trend}<0.001$) and white race (aOR=3.0, 95%CI=2.5-3.6).

Conclusions: There are epidemiologic, tumor and survival differences among HPV-positive tonsil and BOT squamous cell carcinomas. Demographic trends in subsite distribution may be at least partly attributable to history of tonsillectomy. Node-negative BOT tumors exhibit an unexpectedly decreased survival relative to node-negative tonsil and node-positive BOT tumors.

FC04 - HPV Vaccines I

#2316

35 - Advocacy, acceptability and psychology

HPV VACCINE SAFETY PERCEPTIONS AND ADVERSE EVENT REPORTING TRENDS IN THE UNITED STATES

Sonawane K[1], Lin Y[2], Damgacioglu H[3], Zhu Y[4], Fernandez M[5], Montealegre J[6], Ganduglia-cazaban C[7], Li R[8], Lairson D[9], Lin Y[10], Giuliano A[11], Deshmukh A[12]

[1]UTHealth School of Public Health, Houston, United States
[2]UTHealth School of Public Health, Houston, United States
[3]UTHealth School of Public Health, Houston, United States
[4]UTHealth School of Public Health, Houston, United States
[5]UTHealth School of Public Health, Houston, United States
[6]Baylor College of Medicine, Houston, United States
[7]UTHealth School of Public Health, Houston, United States
[8]UTHealth School of Public Health, Houston, United States
[9]UTHealth School of Public Health, Houston, United States
[10]University of Houston, Houston, United States
[11]MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, Tampa, Fl, United States
[12]UTHealth School of Public Health, Houston, United States

Background/Objectives: Safety concern has been identified as a major barrier to the human papillomavirus (HPV) vaccine uptake in the United States (US).[1]Vaccine adverse events (AE) surveillance data plays a critical role in shaping public opinion of vaccine safety.The study objective was to examine time trends in HPV vaccine safety perception among parents of American adolescents and evaluate if the trends in safety perceptions are consistent with HPV vaccine AE reporting data.

Methods: We performed a cross-sectional analysis of a nationally representative immunization survey (the National Immunization Survey [NIS]) and the US vaccine safety surveillance system (the Vaccine Adverse Events Reporting System [VAERS]).[2,3] The NIS respondents were parents of 13-17-year-old adolescents. Adverse events following HPV vaccination were reported to the VAERS by patients, clinicians, and other sources. Time trends in HPV vaccine safety concerns, from 2015 to 2018, were examined nationally and in each of the 50 states and the District of Columbia. We also examined the spontaneous AE reporting trends for HPV vaccination during 2015-2018 and stratified the analysis by non-serious and serious (hospitalizations, disability, and a life-threatening condition or death) type.

Results: From 2015 to 2018, parents of 39,364 unvaccinated adolescents reported their reasons for not initiating the HPV vaccine series. The top five reasons for vaccine refusal were, "not needed or not necessary', "safety concerns', "not recommended', "lack of knowledge', and "not sexually active'. Notably, "safety concerns' as the primary reason for not initiating the HPV vaccine series increased from 13.0% in 2015 to 23.4% in 2018, an increase of 79.9% (Ptrend<0.0001) . A significant rise in HPV vaccine safety concerns occurred in 30 states. The largest increases were observed in California (479.9%), Mississippi (202.5%), South Dakota (243.3%), and Hawaii (258%) (Figure). During 2015-2018, a total of 16,621 AE following HPV vaccination were reported to the VAERS. The AE reporting rate (per 100,000 vaccine doses distributed) decreased from 44.7 in 2015 to 29.4 in 2018 (Ptrend<0.0001). Notably, there was no change in serious AE reporting rate, including those leading to hospitalizations (Ptrend=0.31), disability (Ptrend=0.95), life-threatening condition or death (Ptrend=0.70).

Conclusions: A prominent increase in HPV vaccine safety concerns occurred nationally from 2015 to 2018 counterfactual to the overall decline in AE reporting rate. Our findings highlight an urgent need to combat the rising safety concerns to increase HPV vaccine confidence in the US.

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#2179

5 - HPV prophylactic vaccines

HIGH COVERAGE AND ADHERENCE TO DOSE INTERVALS OF THE NATIONAL SCHOOL-BASED HPV VACCINATION PROGRAM IN SWEDEN 2012-2019

Wang J[1], Nordqvist Kleppe S[2], Hartwig S[3], [4], Koro C[5], Sundström K[6]

[1]KAROLINSKA INSTITUTET, Stockholm, Sweden

[2]Karolinska Institutet, Stockholm, Sweden

[3]Merck & Co., Inc., Kenilworth, Nj, United States

[4], ,

[5]Merck & Co., Inc., Kenilworth, Nj, United States

[6]KAROLINSKA INSTITUTET, Stockholm, Sweden

Background/Objectives: A national school-based free-of-charge HPV vaccination program was implemented in Sweden starting in 2012, targeting girls at ages around 11 years. The 3-dose schedule was utilized during 2012-2014, and the 2-dose schedule started in 2015. The quadrivalent HPV vaccine was used up to mid-2019, later followed by the nonavalent. We investigated quadrivalent vaccine uptake during the 3-dose (2012 to early 2015) and 2-dose (mid-2015 to mid-2019) labelled regimens in adolescent immunization programs. Dosing interval for 3-dose and 2-dose regimens are 0, 2, 6 months; and 0, 6 months, respectively.

Methods: We used the Swedish Total Population Register to define the number of girls born in 2001-2006, i.e. all those who were eligible to receive school-based HPV vaccination between 2012 and March 2019. The mid-time population size over the vaccination period, i.e. at the end of year 2015, was used to define the denominator count of the open underlying cohort (N=335,578). We further used the Swedish National Vaccination Register to identify all girls' HPV vaccination records during 2012-March 2019 (N doses of vaccine administered = 678,031) and linked these to the corresponding individuals by using the unique Swedish personal identification number. We then calculated the vaccine coverage with at least one dose as well as full dose regimens (2 or 3), by birth cohort and county.

Results: The vaccine coverage with at least 1 dose was 79%-83% in birth cohorts 2001-2006, with little variation across the 21 Swedish counties. The 3-dose completion proportions in birth cohorts 2001 and 2002 were 59% and 56% respectively, by the end of study follow-up. A transition from 3-dose to 2-dose schedule was evident in the dose statistics from birth cohorts 2002/2003, and all counties administrated almost exclusively 2-dose schedule from birth cohort 2004 and onwards. The 2-dose completion proportions in birth cohorts 2004 and 2005 were 73% and 74%, respectively, by the end of study follow-up. More than 90% of 2-dose vaccination episodes during the 2-dose regimen followed the recommended time interval of 6-12 months between the first and the second dose (median time in days to dose 2 = 196, IQR= 188-210).

Conclusions: Sweden's 2-dose school-based HPV vaccination program achieves high uptake and has strong adherence to recommended dosing interval.

#1402

5 - HPV prophylactic vaccines

HPV VACCINATION UPTAKE IN BOYS AFTER INTRODUCTION OF GENDER-NEUTRAL HPV VACCINATION IN GERMANY - A RETROSPECTIVE DATABASE ANALYSIS (IMS® VACCINE ANALYZER)

Wähner C[1], Reuschenbach M[2], Mihm S[3], Ohl N[4], Skiebe A[5], Richter H[6, 7, 8, 9]

[1]MSD, Haar, Germany

[2]MSD Sharp & Dohme GmbH, Haar, Germany

[3]MSD Sharp & Dohme GmbH, Haar, Germany

[4]IQVIA Commercial GmbH & Co. OHG, , Frankfurt, Germany

[5]IQVIA Commercial GmbH & Co. OHG, , Munich, Germany

[6]IQVIA Commercial GmbH & Co. OHG, , Frankfurt, Germany

[7], ,

[8], ,

[9], ,

Background/Objectives: Since 2007 HPV vaccination in Germany has been recommended and funded for girls. In June 2018 the German Standing Committee on Vaccination (STIKO) published a gender-neutral recommendation for HPV vaccination for girls and boys 9-14 years old (with catch up to 17). Since January 2019 it is part of mandatory funding by health insurers. The aim of this study was to monitor the monthly uptake of HPV vaccination in boys in Germany and to provide an estimation of the vaccination rate after the first year of funding for boys.

Methods: The study used data from the IMS® Vaccine Analyzer database between January 2018 and December 2019. This database contains anonymized electronic medical vaccination records from a panel of office-based physicians (pediatricians, GPs, gynecologists). The panel was used for nation-wide projections. The primary outcome of the study was the number of boys receiving their first dose by month stratified by physician's specialty. Secondary outcomes included the number of vaccinated girls per month. In addition, HPV vaccination rate for boys in 2019 was estimated by projecting the counts to population census data from the Federal Statistical Office (DESTATIS).

Results: The number of boys 9 to 17 years old vaccinated before the gender-neutral recommendation varied from 98 to 950 per month (first dose January 2018 to May 2018). That number increased from June 2018 (832) to December 2018 (9,670) and further increased sharply with fully implemented reimbursement to 28,691 in January 2019. A further steady increase was observed until May 2019 (52,092) and in the following months numbers remained mostly at the level between 40,000 and 50,000. The number of girls 9 to 17 years old vaccinated (first dose) per month fluctuated between 27,287 and 50,788. One year after the fully implemented reimbursement, the share of boys with at least one dose of HPV vaccination reached 13.8% in the German population of 9- to 17-year-old boys. Almost three-quarter (74.0%) of HPV vaccinations (first dose) in boys were administered by a pediatrician, for girls this share was 52.3%. The proportion vaccinated by a pediatrician in the younger age group (9-14 years old) was 79.1% in boys and 60.1% in girls and in the older age group (15-17 years) 57.9% in boys and 22.8% in girls.

Conclusions: Shortly after the reimbursement of HPV vaccination for boys the number receiving their first dose per month reached the level of girls. This points towards a good acceptance of the gender-neutral recommendation by physicians and parents in the first year, resulting in an estimated vaccination rate for boys (9-17 years) of 13.8% for at least one dose in 2019.

#2407

5 - HPV prophylactic vaccines

TEMPORAL TRENDS IN HPV VACCINATION DURING COVID CONDITIONS IN A TEXAS SAFETY-NET HEALTHCARE SYSTEM

Parker S[1], Mcgee L[2], Daheri M[3], Escobar B[4], Jibaja-weiss M[5], Montealegre J[6]

[1]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine (BCM), Houston, United States

[2]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine (BCM), Houston, United States

[3]Harris Health System, Houston, United States

[4]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine (BCM), Houston, United States

[5]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine (BCM), Houston, United States

[6]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine (BCM), Houston, United States

Background/Objectives: The COVID-19 pandemic led to an interruption in routine pediatric care in the U.S. healthcare system, including HPV vaccination. The Centers for Disease Control and Prevention recommends that children continue to get routine vaccines, including HPV, amid the pandemic (1). Thus many health systems have implemented changes to ensure sustained delivery of the HPV vaccine while maintaining COVID-19 safety measures. Here we assess temporal trends in HPV vaccination rates in a safety-net healthcare system before and during the COVID -19 pandemic and describe targeted interventions to mitigate anticipated declines in vaccine administration.

Methods: Harris Health System is a large safety-net healthcare system serving the Houston area. Since 2016, the health system has been the site of a multilevel intervention that employs several evidence-based strategies to increase HPV vaccination, including provider training and practice facilitation. Using Harris Health databases, we assessed the number of pediatric patients seen and HPV vaccines administered quarterly to patients ages 9-18 at Harris Health between January 1, 2019 and November 31, 2020. We used project and health system administrative records to describe interventions.

Results: The health system had a 60% decrease in patients ages 9-18 seen in the three months after the declaration of the COVID-19 pandemic compared to the same period of time in the prior year (2,043 versus 5,107 patients). However, six months after the declaration of the pandemic, the number of patients increased to 3,502, a 28% decrease compared to the same time period the prior year. Between March 1-May 31, 2019, the ratio of HPV vaccine doses per patient ages 9-18 seen was 0.19, which declined to 0.07 during March 1-May 31, 2020. However, between September 1- November 31, 2020, the ratio returned to 0.19. Interventions used to mitigate the effects of the pandemic included increased vaccine-only appointments, Saturday vaccination clinics and an expanded role for patient navigators that included calling patients to schedule their initial dose.

Conclusions: The number of patients ages 9-18 seen and HPV vaccine doses administered at Harris Health System declined during the COVID-19 pandemic, but both numbers have since increased and are approaching pre-pandemic levels. The ratio of HPV vaccine doses per patient ages 9-18 decreased during the first quarter of the pandemic, but quickly recovered to pre-pandemic levels. The structural changes made within Harris Health prior to and during the pandemic to optimize HPV vaccination rates may have supported the recovery of HPV vaccinations and pediatric patients seen by Harris Health.

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#2281

2 - Epidemiology and natural history

IMPACT OF VACCINATION STRATEGY ON THE RESILIENCE OF HPV16 HERD EFFECT IN UNVACCINATED FEMALES FOLLOWING AN ABRUPT HALT IN VACCINATION: AGE-PERIOD-COHORT ANALYSIS FOLLOWING A COMMUNITY RANDOMISED TRIAL

Gray P[1], Kann H[2], Faust H[3], Elfström M[4], Eriksson T[5], Surcel H[6], Vänskä S[7], Baussano I[8], Lehtinen M[9]

[1]Tampere University, Tampere, Finland

[2]University of Gothenburg, Gothenburg, Sweden

[3]Medical Products Agency (Sweden), Stockholm, Sweden

[4]KAROLINSKA INSTITUTET, Stockholm, Sweden

[5]Tampere University Hospital, Tampere, Finland

[6]University of Oulu, Oulu, Finland

[7]NATIONAL INSTITUTE FOR HEALTH AND WELFARE, Helsinki, Finland

[8]International Agency for Research on Cancer, Lyon, France

[9]Karolinska Institutet, Stockholm, Sweden

Background/Objectives: The implementation of national HPV vaccination programs provides the opportunity to remove disease burden due to high risk HPV infections. However, this depends on the robustness of program implementation, its effectiveness and resilience, which may be severely impacted due to unforeseen circumstances (e.g. overwhelming public health emergencies, changes in vaccine acceptance, political will or program funding). A modelling study1, has indicated that gender-neutral vaccination is more resilient to interruptions in vaccination. We evaluate the resilience provided by gender-neutral versus girls only HPV vaccination strategies to a sudden halt in HPV vaccination.

Methods: In 2007-09, 33 geographically distinct Finnish communities were randomised to receive gender-neutral, girls only or no HPV16/18 vaccination of 1992-95 born early adolescents with approximately 50% vaccination coverage. The subsequent birth cohorts, 1996-97, were not subject to the organised girls-only HPV vaccination program which started in 2014 among the 1998+ birth cohorts. We conducted a cross-sectional serosurvey of 8022 HPV unvaccinated females <23 years old who had donated serum samples to the population-based Finnish Maternity Cohort, between 2005 until the end of 2016. HPV seropositivity was assessed via pseudovirion Luminex serology. Age-period-cohort analysis using the 1990-91 birth cohorts as a reference was conducted to assess the HPV16/18 seroprevalence reduction in the trial birth cohorts (1992-95) and immediately subsequent birth cohorts (1996-97).

Results: In the gender-neutral trial Arm, the HPV16 seroprevalence relative to the 1990-91 birth cohorts, was decreased in the youngest trial birth cohorts (seroprevalence ratio, PR[1994-95]= 0.61 95% CI 0.38-0.98). In the subsequent unvaccinated 1996-97 birth cohorts the estimate appeared to be similar (PR= 0.58 CI 0.29-1.17). In the girls-only Arm, the relative HPV16 seroprevalence showed a tendency to be decreased in the 1994-95 birth cohorts (PR= 0.72 CI 0.49-1.06) and 1996-97 birth cohorts (PR=0.75 CI 0.43-1.30). In the control Arm with no HPV vaccination, the HPV16 seroprevalence ratio approximated unity in the trial and subsequent birth cohorts.

Conclusions: Both gender-neutral and girls-only HPV vaccination may have provided some continued reduction of HPV16 seroprevalence (resilience) to the subsequent unvaccinated cohorts following a complete halt in HPV vaccination. However, our findings appear to verify the predicted expectation, that gender-neutral vaccination provides more resilience. The magnitude of the resilience may be underestimated for populations with a longer time since vaccination program implementation prior to the coverage drop, or with a larger mean age-gap between sexual partners.

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#1535

5 - HPV prophylactic vaccines

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

Joura E[1, 2, 3], Saah A[4], Giuliano A[5]

[1]MEDICAL UNIVERSITY OF VIENNA, Vienna, Austria

[2], ,

[3], ,

[4]Merck & Co., Inc., Kenilworth, Nj, United States

[5]MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, Tampa, Fl, United States

Background/Objectives: The 9vHPV vaccine prevents infection and disease related to the 4 HPV types covered by the quadrivalent HPV (qHPV) vaccine (HPV6/11/16/18) and 5 additional high-risk HPV types (HPV31/33/45/52/58). In a subgroup of female clinical trial participants who underwent cervical surgery (loop electrosurgical excision procedure or conization) after vaccination, we performed a post-hoc analysis on the development of disease related to the 9vHPV vaccine types subsequent to cervical surgery.

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

Results: The post-cervical surgery subgroups included 295 9vHPV vaccine recipients, 493 placebo recipients, and 313 qHPV vaccine recipients (from NCT00543543) who underwent cervical surgery and had ≥6 months' follow-up post-surgery. Prior 9vHPV vaccination was associated with reduction of incidence of HPV6/11/16/18-related condyloma, CIN, VIN, and VaIN at ≥6 months post-surgery by 95.4% (95% confidence interval [CI]: 74.7, 99.8) vs placebo (incidence: 1.3 vs 29.0 per 1000 person-years, respectively) and a reduction of the incidence of HPV31/33/45/52/58-related disease by 86.3% (95% CI: 47.5, 97.8) vs qHPV vaccine (incidence: 2.7 vs 19.4 per 1000 person-years, respectively). Although not statistically significant due to the small number of observed cases, the incidence of high-grade CIN, VIN, and VaIN among 9vHPV vaccine recipients tended to be lower compared with the rates in the relevant comparator groups (HPV6/11/16/18-related high-grade disease incidence was 1.3 [95% CI: 0.0, 7.4] vs 4.4 [95% CI: 1.2, 11.2] per 1000 person years in placebo recipients; and HPV31/33/45/52/58-related high-grade disease incidence was 1.3 [95% CI: 0.0, 7.4] vs 7.7 [95% CI: 2.8, 16.7] per 1000 person-years in qHPV vaccine recipients).

Conclusions: Among women who underwent cervical surgery, prior vaccination with 9vHPV vaccine was associated with reduced incidence of disease.

#2447

5 - HPV prophylactic vaccines

Quadrivalent HPV vaccine effectiveness against anogenital warts: A registry-based study of 1,1 million women in Norway

Nygård S[1], Orumaa M[2], Nygård M[3], Terning Hansen B[4]

[1]CANCER REGISTRY OF NORWAY, , Norway

[2]Cancer Registry of Norway, Oslo, Norway

[3]Cancer Registry of Norway, Oslo, Norway

[4]Cancer Registry of Norway, Oslo, Norway

Background/Objectives: Anogenital warts (AGW) are transmitted sexually and caused by human papillomavirus (HPV). In 2009, Norway initiated routine quadrivalent HPV (qHPV) vaccination for girls at 12-13 years of age to protect against virus types causing cervical cancer, HPV16/18, and HPV 6/11 which cause AGW. Short time lag between infection and AGW allows to investigate the qHPV vaccine effectiveness (VE) against AGW decades before investigating VE against cervical cancer.

Methods: qHPV vaccination registrations and AGW episodes were collected from the Norwegian Immunisation Registry, the Norwegian Prescription Database and the Norwegian Patient Registry for the time period 2006-2016 for birth cohorts 1975-2003. A Cox model was applied to age at first AGW episode, using vaccination status as a time dependent covariate with the effect depending on vaccination age. We also addressed vaccine effectiveness as a function of time since vaccination.

Results: The VE was strongly dependent on vaccination age, with HRs (95% CI) compared to unvaccinated individuals of 0.17 (0.15-0.19), 0.19 (0.13- 0.26), 0.22 (0.17-0.30), 0.46 (0.34-0.60), 0.93 (0.70-1.23), 1.18 (0.73-1.93), and 2.35 (0.98-5.66), for age groups of ≤13, 14-15, 16-17, 18-20, 21-25, 25-30, and 30+ years of age at first vaccination, respectively. A significant VE was seen already two months after the first vaccination dose, as the average number of AGW episodes per month per million vaccinated women was reduced from 332 (95% CI: 256-424) prior to vaccination to 52 (95% CI: 25-95).

Conclusions: When administered before 14 years of age, qHPV vaccination reduces the probability of AGW about six-fold. The effect is decreasing with vaccination age. A significant vaccine effect was seen already two months after the first vaccination dose.

#2307

5 - HPV prophylactic vaccines

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

Luxembourg A[1], Bautista O[2], Saah A[3]

[1]Merck & Co., Inc., Kenilworth, Nj, United States

[2]Merck & Co., Inc., Kenilworth, Nj, United States

[3]Merck & Co., Inc., Kenilworth, Nj, United States

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

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

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

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

#2328

5 - HPV prophylactic vaccines

Immunogenicity of the nine-valent HPV vaccine in people living with HIV and solid organ transplant recipients

Boey L[1], Curinckx A[2], Roelants M[3], Derdelinckx I[4], Van Wijngaerden E[5], De Munter P[6], Vos R[7], Kuypers D[8], Van Cleemput J[9], Vandermeulen C[10]

[1]LEUVEN UNIVERSITY VACCINOLOGY CENTER, Leuven, Belgium

[2]Leuven University Vaccinology Center, Leuven, Belgium

[3]Leuven University Vaccinology Center, Leuven, Belgium

[4]Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium

[5]Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium

[6]Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium

[7]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium

[8]Department of Nephrology and Renal Transplantation, Leuven, Belgium

[9]Department of Cardiology, Leuven, Belgium

[10]LEUVEN UNIVERSITY VACCINOLOGY CENTER, , Belgium

Background/Objectives: The burden of human papillomavirus (HPV) in HIV-infected persons and solid organ transplant (SOT) recipients is high. Clinical trials on HPV vaccines in HIV-infected persons and particularly in SOT recipients have been sparse to date, included low numbers of participants and none of them assessed the nine-valent HPV (9vHPV). We investigated the immunogenicity with respect to HPV types 6/11/16/18/31/33/45/52/58 of the 9vHPV vaccine in HIV-infected persons and recipients of a kidney, lung or heart transplant.

Methods: This is a phase III investigator-initiated study in 100 persons living with HIV (PLWH) (age: 18-45 years) and 171 SOT recipients (age: 18-55 years). The 9vHPV vaccine was administered at day 1, month 2 and month 6. Seroconversion rates to all 9vHPV types and geometric mean titers (GMTs) were assessed at month 7. Predictors of seroconversion and log-transfered titers were assessed with multiple logistic regression.

Results: All PLWH seroconverted for all HPV types, but seroconversion ranged from 46% for HPV45 to 72% for HPV58 in SOT patients. Seroconversion rates were particularly low in lung transplant recipients for HPV18 (38%), HPV31 (43%) and HPV45 (32%). GMTs ranged from 180 to 2985 mMU/ml in PLWH and from 17 to 170 mMU/ml in SOT patients, depending on the HPV type. In the HIV group, significant higher log titers were reached in patients with an African origin compared to Caucasians for all HPV type except 6 and 11. There was no clear effect of the CD4 count, but all participants had a CD4-count of at least 200 cells/µl. In the SOT group, seroconversion was lower for all studied HPV types when the patient received mycophenolate mofetil or tacrolimus, albeit only significant for mycophenolate mofetil. The vaccine is safe and well tolerated in both groups.

Conclusions: Immunogenicity of the 9vHPV vaccine is high in PLWH but suboptimal in SOT recipients. Attention should be paid to HPV vaccination before transplantation.

References: Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, et al. Immunogenicity And Safety Of The Nine-Valent Human Papillomavirus Vaccine In Solid Organ Transplant Recipients And Hiv-Infected Adults. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1897.

#1582

5 - HPV prophylactic vaccines

DESIGN OF A PHASE 3 IMMUNOGENICITY AND SAFETY STUDY EVALUATING 2-DOSE REGIMENS OF 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE WITH EXTENDED DOSING INTERVALS

Teppler H[1, 2], Flores S[3, 4], Mccauley J[5], Bonawitz R[6, 7]

[1]Merck & Co., Inc., Kenilworth, Nj, United States

[2], ,

[3]Merck & Co., Inc., Kenilworth, Nj, United States

[4], ,

[5]Merck & Co., Inc., Kenilworth, Nj, United States

[6]Merck & Co., Inc., Kenilworth, Nj, United States

[7], ,

Background/Objectives: HPV vaccines are widely licensed as 2-dose regimens for young adolescents, with doses administered 6 to 12 months apart. While extending the interval between doses (i.e., to >12 months between Doses 1 and 2) may be necessary in cases of resource constraints or vaccination program disruption, immunogenicity of longer intervals between doses is not well characterized. In 2019, the Strategic Advisory Group of Experts of the World Health Organization proposed countries could adopt an extended interval (3-5 years) between doses in response to programmatic and operational issues, and called for studies to rigorously assess immunogenicity and safety of extended interval dosing (1). This study (Protocol V503-069) will evaluate safety and immunogenicity of 2-dose regimens of 9vHPV vaccine with intervals of 1-5 years between doses in boys/girls vs a standard 3-dose regimen in young women.

Methods: This international, open-label study will enroll participants (planned N=700) into 6 cohorts: Cohort 0 will include boys/girls aged 10-15 years who received 1 dose of commercial 9vHPV vaccine ≥1 year pre-enrollment but did not complete the series; Cohorts 1-4 will include HPV vaccine-naïve boys/girls aged 9-14 years who will receive 2 doses at various intervals (Day 1 and Month 12, 24, 36, or 60 depending on age) and complete dose 2 by age 15; and Cohort 5 will include HPV vaccine-naïve women aged 16-26 years who will receive 3 doses (Day 1, Months 2 and 6). Serum anti-HPV6/11/16/18/31/33/45/52/58 antibodies will be evaluated by competitive Luminex Immunoassay, and geometric mean titers (GMTs) and seropositivity summarized. Noninferiority of GMTs 1 month post last vaccine dose in each of Cohorts 1-4 will be assessed vs Cohort 5 as a primary objective. Antibody responses in Cohort 0 will be characterized at 1 month after Dose 2 (administered at entry), accounting for time between Dose 1 and 2 (co-primary objective). Cohorts will be analyzed sequentially to allow timely assessment of the extended interval dosing regimens. Antibody persistence in Cohorts 1-5 will be assessed through 3 years post last dose. Participants will be followed for injection-site and systemic adverse events (AEs) for 15 days after each vaccination. Data for vaccine-related serious AEs and deaths will be collected throughout the study.

Results: N/A

Conclusions: The design of this study will generate robust clinical safety and immunogenicity data on 9vHPV vaccine extended interval dosing in adolescents, with potential to inform completion of vaccination in individuals who did not complete the recommended series and guide implementation of vaccination programs in resource-limited settings.

References: 1. World Health Organization Strategic Advisory Group of Experts (WHO/SAGE). Meeting of the Strategic Advisory Group of Experts on Immunization, October 2019: conclusions and recommendations. Wkly Epidemiol Rec. 2019;94(47):541-60.

#1738

5 - HPV prophylactic vaccines

DESIGN OF A PHASE 3 EFFICACY, IMMUNOGENICITY, AND SAFETY STUDY OF 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE IN PREVENTION OF ORAL PERSISTENT INFECTION IN MEN

Giuliano A[1], Wilkin T[2], Bautista O[3], Cheon K[4], Connor L[5], Dubey S[6], Group T[7], Luxembourg A[8], Rawat S[9], [10], Vendetti N[11], Tu Y[12]

[1]MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, Tampa, Fl, United States

[2]Weill Cornell Medicine, New York, Ny, United States

[3]Merck & Co., Inc., Kenilworth, Nj, United States

[4]Merck & Co., Inc., Kenilworth, Nj, United States

[5]Merck & Co., Inc., Kenilworth, Nj, United States

[6]Merck & Co., Inc., Kenilworth, Nj, United States

[7]Merck & Co., Inc., Kenilworth, Nj, United States

[8]Merck & Co., Inc., Kenilworth, Nj, United States

[9]Merck & Co., Inc., Kenilworth, Nj, United States

[10], ,

[11]Merck & Co., Inc., Kenilworth, Nj, United States

[12]Merck & Co., Inc., Kenilworth, Nj, United States

Background/Objectives: HPV-related head and neck cancers (HNCs) create significant disease burden and disproportionately impact men [1]. Seven high-risk HPV types (HPV16/18/31/33/45/52/58) covered by the 9vHPV vaccine cause >90% of HPV-related HNCs [2]. While HPV oral infection is a known HNC risk factor and persistent infection is a necessary step toward development of HPV-related cancer, there are no preventive medicines, vaccines, or early screenings for HPV-related HNCs [3-6]. The current study (NCT04199689) is designed to demonstrate the efficacy of 9vHPV vaccine in preventing HPV vaccine type-related oral persistent infection.

Methods: In this double-blind, placebo-controlled, international study, men aged 20-45 years (planned N=6000) are randomized 1:1 to receive 9vHPV vaccine or placebo on Day 1, Month 2, and Month 6. The primary objective is to demonstrate that 9vHPV vaccination reduces the incidence of the primary efficacy endpoint (HPV16/18/31/33/45/52/58-related oral persistent infection ≥6 months). The secondary objectives are to 1) demonstrate that 9vHPV vaccination reduces the incidence of HPV6/11-related oral persistent infection ≥6 months; 2) summarize HPV vaccine type antibody response (GMT and seroconversion percentage); and 3) evaluate 9vHPV vaccine safety and tolerability in the study population. Oral rinse and gargle samples will be collected on Day 1, Month 7, Month 12, and every 6 months thereafter and analyzed for DNA of 14 HPV types by a multiplex type-specific PCR assay. Sera will be collected on Day 1 and Month 7 (all participants) and Months 12, 24, 36, and 42 (1200 participant subset), and anti-HPV type-specific antibody titers analyzed by competitive Luminex Immunoassay. All participants who received ≥1 dose will be followed for injection-site and systemic AEs (Days 1-15 postvaccination), serious AEs regardless of causality through 6 months after the last vaccination, and death and vaccine-related serious AEs throughout the study. Primary efficacy and immunogenicity analyses will be performed in participants who received 3 doses and were baseline seronegative and PCR negative from baseline through Month 7 for the relevant HPV type. The study is case-driven, and efficacy analyses will be conducted on accrual of ≥20 primary efficacy endpoint cases. The study was initiated February 27, 2020, and is estimated to be completed in 2024.

Results: N/A

Conclusions: If successful, data from this ongoing randomized, placebo-controlled study would provide strong evidence that the 9vHPV vaccine can prevent HPV-related HNC. This would represent a significant medical advancement and emphasize the importance of HPV vaccination regardless of gender.

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HN05 - Submitted Papers II

#2045

29 - HPV and oropharynx / Head and neck cancer

ZNF671 - A PROMISING EPIGENETIC BIOMARKER FOR IMPROVED DETECTION OF HEAD AND NECK CANCER IN NON-INVASIVE SPECIMEN

Hums A[1], Priese J[2], Erler T[3], Stieber B[4], Jansen L[5], Durst M[6], Guntinas-lichius O[7], Schmitz M[8], Hansel A[9]

[1]ONCGNOSTICS GMBH, Jena, Germany

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

[3]oncgnostics GmbH, Jena, Germany

[4]oncgnostics GmbH, Jena, Germany

[5]DEPARTMENT OF GYNAECOLOGY, JENA UNIVERSITY HOSPITAL, , Germany

[6]JENA UNIVERSITY HOSPITAL, Jena, Germany

[7]Department of Otorhinolaryngology, Jena University Hospital, Jena, Germany

[8]ONCGNOSTICS GMBH, Jena, Germany

[9]ONCGNOSTICS GMBH, Jena, Germany

Background/Objectives: Head and neck squamous cell carcinomas (HNSCC) are mainly diagnosed at advanced tumour stage after the onset of symptoms. Timely detection would significantly improve the options for successful treatment and thus contribute to a decrease in the mortality observed for this group of carcinomas. Consequently, non-invasive diagnostic tools for early and precise detection need to be established. We have studied the DNA methylation of the promoter/5' region of the ZNF671 gene, which is already established as a marker for use in cervical cancer diagnostics. Alteration of the methylation status for ZNF671 is also known for head and neck tumours. Therefore, we developed a QPCR assay for the detection of tumour-specific DNA methylation of the promoter/5' region of ZNF671 from primary HNSCC tumour tissue as well as in non-invasive specimen such as buccal swabs and saliva.

Methods: Different sample sets from HNSCC patients and healthy test persons were collected: (1) fresh-frozen tissue samples (63x HNSCC; 56x controls), (2) buccal swabs (31x HNSCC; 33x controls), and (3) tissue and saliva from 26 further HNSCC patients. The specimens were collected at the Department of Otorhinolaryngology, Jena University Hospital. Validation of the marker ZNF671 (bisulphite-specific reference Beta-actin, ACTB) was performed using methylation-specific QPCR. Isolated genomic DNA was bisulphite-converted before use in QPCR assay. Calculations of the clinical sensitivity and specificity as well as methylation level in relation to the reference were used for performance evaluation of the assay.

Results: In the tissue sample set (1) ZNF671 yielded 71% clinical sensitivity (45/63 patients ZNF671-positive) and 98% specificity (1/56 controls ZNF671-positive). In swab samples (2) ZNF671 showed slightly weaker detection, resulting in a clinical sensitivity of 64% (20/31 patients positive) and a specificity of 87% (4/33 controls positive). In group 3 the clinical sensitivity for ZNF671 in saliva samples reached 96% (24/25 patients positive) and 96% (25/26 patients positive) in tumour tissue samples. For 21 patients of group 3 both, tumour tissue and saliva were available. In 20 of these 21 patients (=95%), matching results between tissue and saliva were obtained. Results from a corresponding control group are not yet available. First results from healthy control group from saliva sampling are expected in February 2021.

Conclusions: ZNF671 may be utilized as a reliable HNSCC marker. Preliminary results from validation and recent patient samples showed that ZNF671 was robustly detectable in all three tested specimen types: tissue, swab and saliva. Utilization of saliva samples for local and easy-to-use sample collection for application in a cancer-specific multiplex assay will be useful as an in vitro diagnostic strategy in secondary and tertiary prevention.

#2320

29 - HPV and oropharynx / Head and neck cancer

A Deficiency in the ATM-mediated DNA Damage Response Contributes to the DNA Repair Defect of HPV-positive Head and Neck Cancer

Rieckmann T[1], Köcher S[2], Zech H[3], Gatzemeier F[4], Christiansen S[5], Kriegs M[6], Petersen C[7], Rothkamm K[8]

[1]UNIVERSITY MEDICAL CENTER HAMBURG-EPPENDORF, Hamburg, Germany

[2]University Medical Center Hamburg-Eppendorf, , Germany

[3]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[7]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[8]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background/Objectives: Radiotherapy is a mainstay in the treatment of locally advanced head and neck cancer (HNC) and patients with HPV-positive (HPV+) disease show favorable survival. We had shown previously that HPV+ HNC cell lines are characterized by enhanced radiosensitivity caused by a defect in the repair of DNA double-strand breaks (DSB), the most toxic radiation-induced lesions. Since then various publications have suggested varying mechanisms, such as a defect in homologous recombination (HR) or the dysregulated expression of different DSB repair factors but evidence was mostly based on very few cell lines.

Methods: Quantification of repair proteins by Western blot; functional analyses in 3 radiosensitive HPV+ vs. 2 radioresistant HPV- cell lines; ATM inhibition by KU55933; assessment of cell survival after irradiation or PARP inhibition by colony formation assay; analysis of cell cycle; quantification of DSBs by immunofluorescence microscopy of DSB repair foci; analysis of ATM activity by Western blot and assessment of radiation induced DNA end resection.

Results: Comparing the expression of DSB repair factors - some of them reported to cause the DSB repair defect of HPV+ HNC - in 6 HPV+ vs. 5 HPV- HNC cell lines, we could not confirm most of the published differences. Furthermore, HPV+ HNC strains did not demonstrate enhanced sensitivity towards PARP-inhibition questioning the suggested general HR-defect. Interestingly, the expression screen revealed only minimal levels of the central DNA damage response kinase, ATM, in the two most radiosensitive HPV+ cell lines. We therefore tested whether insufficient ATM activity may contribute to the enhanced cellular radiosensitivity. Irrespective of their ATM expression level, radiosensitive HPV+ HNC cells displayed DSB repair kinetics similar to ATM deficient cells. Upon ATM inhibition, HPV+ cell lines showed only a marginal increase in average residual radiation induced γH2AX repair foci (1.33x) as compared to HPV- ones (4.42x) and only little effect on cell cycle arrest. In line with these observations, ATM inhibition sensitized HPV+ HNC strains to less extent towards radiation than HPV-, resulting in similar levels of sensitivity. Unexpectedly, assessment of ATM target phosphorylation after radiation did not reveal an obvious difference between HPV+ and HPV- cells and radiation-induced ATM mediated DNA end resection was also similar in both cell types.

Conclusions: DNA repair kinetics and a reduced effectiveness of ATM inhibition clearly point to an impaired ATM orchestrated DNA damage response in HPV+ HNC cells but since ATM itself is apparently functional the molecular mechanisms need to be further explored.

#2283

29 - HPV and oropharynx / Head and neck cancer

QUANTIGENE-MOLECULAR PROFILING HISTOLOGY ASSAY: HPV ONCOGENE AND BIOMARKER MRNA DETECTION AND QUANTIFICATION FOR HNSCC SAMPLES

Thies S[1], Skof A[2], Schäfer N[3], Cherif S[4], Klinghammer K[5], Albers A[6], Kaufmann A[7]

[1]Charité - Clinic for Gynecology , Berlin, Germany

[2]CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

[3]Charité - Clinic for Gynecology , Berlin, Germany

[4]Charité - Clinic for Gynecology , Berlin, Germany

[5]Charité - Clinic for Oncology and Hematology, Berlin, Germany

[6]Charité - Clinic for ENT, Berlin, Germany

[7]CLINIC FOR GYNECOLOGY, CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

Background/Objectives: Human papillomaviruses (HPV) not only cause malignant changes in the human anogenital area but also in other body regions, such as the head-and-neck (ENT) area. Without the possibility of targeted smears, it is difficult to determine whether a cellular change in the oral cavity is caused by HPV infection or toxic substances. Knowledge of HPV involvement, thus expression of HPV oncogenes and related cellular biomarkers are important for patient staging and treatment, as HPV positive tumors have a better prognosis due to their biological characteristics. Based on the latest data of the QuantiGene-molecular-histology assay (QG-MPH) detecting cervical dysplasia with high accuracy, its feasibility should be extended to other HPV-related diseases. To confirm whether samples from other body regions and different material composition can be used, characterized HNSCC's (Head and Neck Squamous Cell Carcinoma"s) tissues were selected.

Methods: ï»¿The QG-MPH is a multiplexed mRNA quantifying assay that combines the detection of HPV genotype-specific oncogene expression with the expression of cellular biomarkers for proliferation, cancer stem cells, and tumor markers. To evaluate its applicability for samples of other material properties than gynecological pap smears, we chose characterized primary HNSCC's, which were transplanted onto nude mice and were established as patient derived xenografts (PdX). The PdX tumors (n=14) were embedded into paraffin, sections sliced, lysed, and analyzed by QG-MPH. With the Luminex bead-based QuantiGene 2.0 technology platform (ThermoFisher Scientific) quantification of the most informative mRNA species (HPV E6/E7, p16, p53, STMN1, SOX2, TERT) was done simultaneously.

Results: According to internal control (human housekeeping gene ACTB) all 14 analyzed HNSCC-PdX were found to be valid concerning material content. HPV+ could be detected in six cases by E7/E6 oncogene mRNA expression (5xHPV16, 1xHPV33) corresponding to PCR-based HPV genotyping. Eight samples demonstrated HPV-. p16 was upregulated in all 6/6 HPV+ and in 4/8 HPV- PdX. p53 was strongly expressed in all PdX. Ki67 showed a trend for stronger expression in HPV+ HNSCC. A significantly different expression between HPV+ and HPV- PdX was found for tumor markers Stathmin, Sox, and TERT.

Conclusions: Measurement of E6/E7 mRNA expression identifies true HPV-induced HNSCC. Increased HPV-independent p16 expression was also identified, which may be misleading in HNSCC tumor classification. These results strongly indicate that the QG-MPH may be useful to analyze and characterize HPV-associated samples from HNSCC and potentially other body regions and of different diagnostic materials.

#2309

29 - HPV and oropharynx / Head and neck cancer

RADIATION-INDUCED UPREGULATION OF DNA SENSING PATHWAYS IS DEPENDENT ON HPV STATUS OF PHARYNGEAL SQUAMOUS CELL CARCINOMA

Levpuscek K[1], Jesenko T[2], Sersa G[3], Cemazar M[4], Strojan P[5]

[1]Institute of Oncology Ljubljana and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[2]Institute of Oncology Ljubljana and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[3]Institute of Oncology Ljubljana and Faculty of Health Sciences, University of Ljubljana, Ljubljana, Slovenia

[4]Institute of Oncology Ljubljana and Faculty of Health Sciences, University of Primorska , Ljubljana, Izola, Slovenia

[5]Institute of Oncology Ljubljana and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Background/Objectives: Human papillomavirus (HPV) positive oropharyngeal squamous cell carcinoma (OPSCC) represents a unique clinical entity distinct from HPV negative pharyngeal squamous cell carcinomas (PSCC). One of the main differences is that HPV positive OPSCC responds better to irradiation (IR) than HPV negative PSCC, however the exact mechanisms are still unknown. It was previously shown that the HPV oncoproteins E6 and E7 antagonize cytosolic DNA sensors, which can mediate cytokine production through several signaling pathways and consequently impact the immune response. The latter is an important component of tumor radiosensitivity. The aim of our study was to investigate the involvement of DNA sensing pathways in response to IR in HPV positive OPSCC and HPV negative PSCC cell lines.

Methods: Radiosensitivity of PSCC (FaDu and 2A3) and OPSCC (UM-SCC-6 and UPCI:SCC090) cell lines with different HPV status was determined by metabolic PrestoBlue viability test. Gene expression of different DNA sensors and cytokines was determined after IR with different single doses (0, 4 and 8 Gy). Total RNA was isolated after 24 as well as 48 hours and reverse transcribed into cDNA. The expression of DNA sensors (cGAS, STING, RIG-I, DAI, IFI16, DDX60), cytokines (IFNß, TNFa, IL1ß) and HPV viral load were determined using qRT-PCR.

Results: Difference in radiosensitivity was observed between HPV positive and HPV negative OPSCC but not in PSCC cell lines. The upregulation of expression of cytosolic DNA sensors and cytokines was dose-, time-dependent and HPV status dependent. After IR, cytosolic DNA sensors DAI and RIG-I were upregulated in HPV negative OPSCC and PSCC but not in HPV positive cell lines. The expression of DAI was significantly higher in HPV negative FaDu than in the HPV negative UM-SCC-6 cell line. The expression of cytokines IFNßand IL1ß after IRwas significantly upregulated in HPV negative cell lines. Expression of DNA sensors and cytokines differed based on the level of expression of HPV oncoproteins E6 and E7; namely, it was significantly higher in HPV positive 2A3 cell line, which had lower levels of expression of HPV oncoproteins compared to the HPV positive UPCI:SCC090 cell line.

Conclusions: Our findings suggest that the expression of cytosolic DNA sensors and cytokines differs in response to IR in OPSCC and PSCC cell lines based on HPV infection, which indicates a possible role of cytosolic DNA sensors in radiosensitivity of HPV positive OPSCC cell lines. Further studies are needed to elucidate the complexity of mechanisms involved in DNA sensing pathways concerning HPV and IR.

#1549

22 - Diagnostic procedures / management

ANATOMIC CLASSIFICATION OF HEAD AND NECK CANCERS BASED ON ICD CODES IN THE CONTEXT OF A GLOBAL CROSS-SECTIONAL STUDY TO ASSESS THE FRACTION OF HEAD AND NECK CANCERS ATTRIBUTABLE TO HUMAN PAPILLOMAVIRUS (THE BROADEN STUDY)

Waterboer T[1], Mehanna H[2], Alemany L[3], Giuliano A[4], Mirghani H[5], Gómez D[6], Lara N[7], Morais E[8], Kothari S[9], Roberts C[10], Mirghani H[11]

[1]GERMAN CANCER RESEARCH CENTER (DKFZ), Heidelberg, Germany

[2]Institute of Head & Neck Studies and Education (InHANSE), University of Birmingham, Birmingham, United Kingdom

[3]Cancer Epidemiology Research Program, Catalan Institute of Oncology - IDIBELL, Hospitalet de Llobregat; and CIBERESP, Barcelona, Spain

[4]MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, Tampa, Fl, United States

[5]HÔPITAL EUROPÉEN GEORGES-POMPIDOU, ORL, Paris, France

[6]IQVIA, Real World Solutions, Barcelona, Spain

[7]IQVIA, Real World Solutions, Barcelona, Spain

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

[9]Center for Observational and Real-World Evidence, Merck & Co., Inc., Kenilworth, Nj, United States

[10]Center for Observational and Real-World Evidence, Merck & Co., Inc., Kenilworth, Nj, United States

[11]HÔPITAL EUROPÉEN GEORGES-POMPIDOU, ORL, Paris, France

Background/Objectives: The BROADEN study is a global cross-sectional study to assess the past (10 years ago) and current fractions of head and neck cancers (HNC) attributable to human papillomavirus (HPV), per anatomic site.1 Currently, HPV is an accepted cause of oropharyngeal cancer with a growing literature suggesting HPV may have a causal role in the etiology of other HNCs. Investigating HPV in the development of HNCs requires consistent classification of anatomic sites within the head and neck over time. The 10th revision of the International Classification of Diseases code set (ICD-10) was released in 2014, including major structural changes versus earlier ICD-9 such as the use of alphanumeric categories instead of numeric ones, and is progressively being adopted. However, guidance on the equivalences between both code sets for HNCs is limited. In addition, some of the codes and definitions do not allow a clear distinction between anatomic sites, leading to a lack of general consensus on the criteria to group codes per anatomic site in HNC.2, 3 The objective of this work was to generate a table of equivalences between ICD-9 and ICD-10 codes for HNC, and to group these codes per anatomic site.

Methods: The diagnosis codes of HNCs available in the ICD-9 and ICD-10 code sets were reviewed and compared, and a table of equivalences per anatomic site was generated. The correlations and inconsistencies between code sets were reviewed, complemented and discussed by a group of epidemiologists and clinicians with expertise in HPV and HNC, until consensus agreement was reached.

Results: Table 1 shows the equivalences between ICD-9, ICD-10 codes and anatomic sites, not including codes related to overlapping lesions.

Conclusions: This novel consensus classification of HNCs per anatomic site fills a current unmet need in HPV research and provides a practical tool for use in the BROADEN study, and in future research.

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#2274

28 - Oral HPV infection

Oral HPV16 DNA as a screening tool to detect early oropharyngeal squamous cell carcinoma.

Tang K[1], Vasani S[2], Menezes L[3], Taheri T[4], Hughes B[5], Kenny L[6], Punyadeera C[7]

[1]QUEENSLAND UNIVERSITY OF TECHNOLOGY, Brisbane, Australia

[2]Royal Brisbane and Women's Hospital, Brisbane, Australia

[3]Queensland University of Technology, Brisbane, Australia

[4]Royal Brisbane and Women's Hospital, Brisbane, Australia

[5]Royal Brisbane and Women's Hospital, Brisbane, Australia

[6]Royal Brisbane and Women's Hospital, Brisbane, Australia

[7]Queensland University of Technology, Brisbane, Australia

Background/Objectives: Given that the incidence of human papillomavirus (HPV)-driven oropharyngeal squamous cell carcinoma (OPSCC) is rapidly increasing in developed countries, there is an interest in developing non-invasive predictive biomarkers to early detect HPV-driven OPSCC.

Methods: A total of 665 cancer-free individuals were recruited and oral HPV16 DNA positivity in those individuals was determined. Individuals with (n=9) or without (n=12) oral HPV16 infections at baseline were followed for a median duration of 24 months. Individuals with persistent oral HPV16 infection (≥ 30 months) were invited for clinical examination of their oral cavity and oropharynx by an otolaryngologist.

Results: Oral HPV16 DNA was detected in 12 out of 650 individuals (1.8%; 95% CI: 1.0-3.2). Of the 3 individuals with persistent oral HPV16 infection, the first individual showed no clinical evidence of pathology. The second individual was diagnosed with a p16INK4a positive 2mm tonsillar squamous cell carcinoma (T1N0M0). The third individual was found to have a mildly dysplastic lesion in the tonsillar region that was negative for p16INK4a expression and HPV16 DNA and she continues to have HPV16 DNA in her saliva.

Conclusions: Taken together, this study gives unique insights into the use of serial saliva sampling to detect HPV as a screening tool for OPSCC. Furthermore, it also builds the scientific foundation for initiating a screening trial to combat the rising incidence of OPSCC.

#2409

29 - HPV and oropharynx / Head and neck cancer

the role of transoral robotic surgery in head and neck carcinoma of unknown primary. A single centre experience.

Lee E[1], Jack F[2], Nikoleta S[3], Brunet A[4], Jean-pierre J[5], Ann S[6], Asit A[7]

[1]Kings College London, London, United Kingdom

[2]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[3]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[4]Guy's and St Thomas' NHS Foundation Trust, , United Kingdom

[5]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[6]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Background/Objectives: Carcinoma of Unknown Primary (CUP) accounts for 5% of head and neck malignancies. The majority arise from <1cm HPV positive squamous cell carcinomas in oropharyngeal lymphoid tissue. Patients with no identified primary receive bilateral radiotherapy associated with immediate and delayed complications. Primary tumour identification allows directed therapy reducing complications. Transoral robotic surgery (TORS) tongue base mucosectomy, completely excises the lingual lymphoid tissue providing greater detection rates than traditional biopsy. . This project reports a single centre experience of TORS as a diagnostic and therapeutic tool in CUP.

Methods: This retrospective study reports a single centre experience at a central London teaching hospital between January 2018 and January 2021. All patients presenting with CUP who received TORS were included. All patients were discussed in the MDT. Decision for tonsillectomy, tongue base mucosectomy or both and subesquent treatment was determined by MDT discussion. Patients with identified tumours received site specific therapy or primary surgical resection. Patients without identified primary received wide field radiotherapy with or without adjutant chemotherapy.

Results: 22 Patients with CUP underwent TORS between January 2018 and January 2021. 19(86%) received bilateral tonsillectomy and tongue base mucosectomy. 3(14%) received tongue base mucosectomy alone. A primary tumour was identified in 17/22 (77%) patients (7 tonsil, 4 tongue base, 6 glossotonsillar sulcus). 13/17 patients had lateralising disease. Mean tumour diameter was 12.1mm (7-35mm) tonsil, 12.9mm (7-11mm) tongue base, 12.2mm (1.5-21mm) glossotonsilar sulcus. Mean depth of invasion was 4.3mm (3-10mm) tonsil, 4.4mm (3.5-5.mm) tongue base, 4mm (1.5-4mm) glossotonsilar sulcus.3/17 patient had multifocal disease. 4/22 patients had HPV negative disease identified in the neck. 2/17 identified primaries were HPV negative. Of the 17 patients with identified primary tumours 7 underwent primary surgical treatment with TORS + neck dissection (5 enrolled in PATHOS). 2 patients had clear margins and N1 neck disease and received no further treatment. 3 patients enrolled in arm B and 1 in arm C due to ECS. 1 patient received PORT outside of PATHOS.2 patients treated with primary CRT required salvage neck dissection.

Conclusions: TORS provides favourable primary detection rates and may allow total tumour excision with negative margins. Within the context of treatment de-escalation trials this may allow adjuvant therapy to be avoided. Transoral robotic assisted tongue base mucosectomy and tonsillectomy have diagnostic and therapeutic contributions to patients with carcinoma of unknown primary.

#2386

29 - HPV and oropharynx / Head and neck cancer

Targeted therapy with FGFR and PI3K inhibitors on HPV positive and negative tonsillar and base of tongue cancer lines with and without corresponding mutations

Holzhauser S[1], Wild N[2], Zupancic M[3], Ursu R[4], Bersani C[5], Näsman A[6], Kostopoulou O[7], Dalianis T[8]

[1]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

[2]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

[3]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

[4]Dept. of Microbiology, University of Medicine and Pharmacy, Grigore T. Popa, Iasi, Romania

[5]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

[6]KAROLINSKA INSTITUTET, Stockholm, Sweden

[7]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

[8]KAROLINSKA INSTITUTE, Stockholm, Sweden

Background/Objectives: Human papillomavirus positive (HPV+) tonsillar and base of tongue squamous cell carcinoma (TSCC/BOTSCC) generally have a favorable outcome, but upon relapse treatment options are limited. FGFR3 and PIK3CA are often mutated in HPV+ cancer and we have also previously tested HPV+ and one HPV- TSCC/BOTSCC cell lines without such mutations for their sensitivity towards FGFR and PI3K inhibitors respectively. In this report we have extended such studies to HPV+ TSCC/BOTSCC cell lines with and without such mutations, and also tested additional targeted inhibitors and also plan to test PI3K and FGFR inhibitors in combination with cisplatin and docetaxel.

Methods: HPV+ CU-OP-2, -3 and -20 and HPV- CU-OP-OP-17 were tested by competitive allele-specific TaqMan-PCR (CAST-PCR) for presence/absence of frequently occurring FGFR3 and PIK3CA mutations. All cell lines including were then treated with FGFR inhibitor AZD4547, JNJ-42756493 and PI3K inhibitors BEZ235 and BYL719 alone, or in different combinations. The cell lines will also be tested for their sensitivity to cisplatin and docetaxel alone and in combination with the FGFR and PI3K inhibitors. Viability was analyzed by a WST-1 assay, while proliferation, apoptosis and cytotoxicity were tested by the IncuCyteTM S3 Live® Cell Analysis System.

Results: HPV+ CUOP-2 exhibited both an FGFR and PI3K mutation, while CUOP-20 only exhibited a PI3K mutation, while none of the other cell lines had such mutations. All cell lines were sensitive to single treatments with FGFR and PI3K inhibitors to some extent, and all were more sensitive to FGFR/PI3K inhibitor combination treatments. However, sensitivity was/was not correlated to presence of FGFR/PI3K mutations. The cell lines are now be tested for their sensitivity to cisplatin and docetaxel alone and in combination with FGFR/PI3K inhibitors and cisplatin and docetaxel.

Conclusions: FGFR and PI3K inhibitors exhibited an inhibitory effect on the viability of both HPV+ and HPV- CU-OP cells, irrespective if they had FGFR and PI3K mutations or not, and sensitivity did not increase dependent on the presence of FGFR or PI3K mutations in the cell lines. Moreover, similar to our previous experience combinations of FGFR and PI3K targeted therapy enhanced the sensitivity of all cell lines. Data on the chemotherapeutic drugs alone and combined with the inhibitors will be presented.

FC05 - Epidemiology

#2177

2 - Epidemiology and natural history

PREVALENCE OF HUMAN PAPILLOMAVIRUS AMONG FEMALES OLDER THAN RECOMMENDED AGE FOR VACCINATION BY BIRTH COHORT, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, UNITED STATES, 2003â€'2016

Vahle K[1], Gargano J[2], Lewis R[3], Querec T[4], Unger E[5], Bednarczyk R[6], Markowitz L[7]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States

[2]Centers for Disease Control and Prevention, Atlanta, Georgia, United States

[3]CENTERS FOR DISEASE CONTROL AND PREVENTION, Atlanta, United States

[4]Centers for Disease Control and Prevention, Atlanta, Georgia, United States

[5]Centers for Disease Control and Prevention, Atlanta, Georgia, United States

[6]Emory University, Atlanta, Georgia, United States

[7]CENTERS FOR DISEASE FOR DISEASE CONTROL AND PREVENTION, Atlanta, United States

Background/Objectives: Apparent associations between HPV prevalence and age observed in cross-sectional studies could be due to cohort effects. Using data from National Health and Nutrition Examination Surveys (NHANES) 2003â€'2016, we evaluated overall and birth cohort-specific HPV prevalences by age among 27â€'59 year-old females born in 1950â€'1979.

Methods: NHANES data from females with adequate HPV typing results from self-collected cervicovaginal swabs were analyzed. Prevalences of any HPV (any of 37 types detected by Linear Array), high-risk-HPV (HR-HPV, HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68), and non-HR-HPV (HPV6/11/26/40/42/53/54/55/61/62/64/67/69/70/71/72/73/81/82/83/84/89/IS39) were estimated by 3-year age groups overall as well as stratified by birth cohort (1950-59, 1960-69, 1970-79). The average percent change (APC) in HPV prevalence by 3-year age group was calculated using prevalence ratios from log-binomial models. Separate models were run by individual characteristics to evaluate the extent to which other HPV risk factors might confound or mediate the association between age and prevalence.

Results: The study sample included 7902 females with valid HPV typing results; of these, 1942 were born in the 1950s (ages 45-59 at time of NHANES participation), 2976 were born in the 1960s (ages 36-56), and 2984 were born in the 1970s (ages 27-44). Overall, prevalence of any HPV declined from 49.9% in 27-29 year-olds to 33.8% in 57-59 year-olds [APC: -2.82 per 3-year age group (95% confidence interval (CI): -4.02%, -1.60%)] as did prevalence of HR-HPV [APC: -6.19% (95% CI: -8.09%, -4.26%)] and non-HR-HPV [APC: -2.00% (95% CI: -3.48%, -0.51%)]. After adjusting for various demographic and sexual behavioral characteristics, some APC estimates changed in magnitude, but the inverse relationships between age and HPV prevalence remained and were significant for any and HR-HPV. By birth cohort, declines by age group were seen in prevalence of any HPV, HR-HPV, and non-HR-HPV for those born in the 1950s and 1970s and in any HPV and HR-HPV for those born in the 1960s (APC range: -14.08% - 0.06%).

Conclusions: Declines in HPV prevalence with age cannot be explained by birth cohort differences alone, as the association was observed across all birth cohorts. These findings regarding age trends in HPV prevalence are consistent with biological explanations, such as clearance or immune control of infections, and behavioral explanations, such as lower rates of exposure with age.

#2253

2 - Epidemiology and natural history

Evolution of cervical high grade dysplasia during pregnancy and post partum : what role does the delivery route play ?

Jacot-guillarmod M[1], Yvan G[2], Patrice M[3]

[1]Mother-and-Child Department CHUV, Lausanne, Switzerland

[2]Mother-and-Child Department CHUV, Lausanne, Switzerland

[3]Mother-and-Child Department CHUV, Lausanne, Switzerland

Background/Objectives: The evolution of high-grade cervical dysplasia during pregnancy and its relation to the route of delivery remain unclear. The management of pregnant women diagnosed with high-grade dysplasia is a recurrent challenge. The aim of our study was to observe the evolution of high-grade cervical dysplasia during the postpartum period and to determine the impact of the route of delivery on said dysplasia.

Methods: We retrospectively enrolled 79 patients diagnosed with high-grade lesions, either cytologically by HSIL or histologically with cervical intraepithelial neoplasia (CIN2+) during pregnancy between January 2000 and October 2017. Postpartum regression was defined cytologically or histologically by a one-degree reduction in severity from the antepartum diagnosis. The route of delivery, parity, diabetes, smoking, postpartum control delay, and maternal age (>30 years) were included in a logistic regression model in order to analyze their influence on the regression of high-grade cervical dysplasia.

Results: Diagnoses of prenatal high-grade cervical dysplasia were established by cytology in 87% of cases (69/79) and confirmed by histology in 45% of those (31/69). The overall regression in our cohort was 43% (34/79). The regression rate in the vaginal-route group was 41% (22/54), and that in the C-section group was 48% (12/25) (p = NS). Univariate analysis revealed that nulliparity was a unique, significant factor (odds ratio (OR) = 2.76; 95% confidence intervals (95%CI): 1.02-7.49; p = 0.037). This factor did not reveal a significant influence when included in a logistic regression model.

Conclusions: The regression rate in our study was high, at 43%, for high-grade cervical lesions postpartum, regardless of the route of delivery. However, we observed that nulliparity is associated with a higher regression rate.

#2170

2 - Epidemiology and natural history

PREVALENCE OF HUMAN PAPILLOMAVIRUS AMONG FEMALES OLDER THAN RECOMMENDED AGE FOR VACCINATION BY NUMBER OF LIFETIME PARTNERS, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, 2003-2016

Lewis R[1], Vahle K[2], Gargano J[3], Querec T[4], Unger E[5], Markowitz L[6]

[1]CDC, Atlanta, Ga, United States

[2]CDC, Atlanta, Ga, United States

[3]CDC, Atlanta, Ga, United States

[4]CDC, Atlanta, Ga, United States

[5]CDC, Atlanta, Ga, United States

[6]CENTERS FOR DISEASE FOR DISEASE CONTROL AND PREVENTION, Atlanta, United States

Background/Objectives: Human papillomavirus prevalence is consistently associated with age and number of lifetime sex partners (LTSP), but the impact of birth cohort is less well understood. Using data from National Health and Nutrition Examination Surveys (NHANES) 2003-2016, we estimated high-risk (HR) HPV prevalence by age among 27-59-year-old females born in 1950-1979 with ≤5 and >5 LTSP, overall and by birth cohort, to evaluate age-specific patterns in prevalence by number of LTSP and birth cohort differences in these patterns.

Methods: Cervicovaginal swabs were self-collected and tested for 37 HPV types using Roche Linear Array assay. Data from females with adequate typing results were analyzed. HR-HPV prevalence (HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68, types targeted by clinical HPV tests) was estimated by 3-year age group among females with ≤5 and >5 LTSP. Average percent changes (APC) in prevalence by 3-year age were calculated using prevalence ratios from log-binomial models. Differences in age-specific patterns of prevalence by number of LTSP were evaluated by testing an age group (treated as continuous) x LTSP (binary) interaction term in log-binomial models. The analysis was repeated for three 10-year birth cohorts (1950s, 1960s, 1970s).

Results: Among females with ≤5 LTSP, prevalence decreased by 4.31% on average per increase in 3-year age group (APC: -4.31%, 95% CI: -7.27%, -1.27%) from 16.3% (95% CI: 9.8, 25.7) among 27-29-year-olds to 10.8% (95% CI: 7.1, 16.3) among 57-59-year-olds. Prevalence in each age group was higher among females with >5 LTSP than those with ≤5 LTSP. Prevalence among females with >5 LTSP decreased by 6.53% on average per increase in 3-year age group (APC: -6.53%, 95% CI: -9.12%, -3.87%) from 33.7% (95% CI: 22.1, 47.7) among 27-29-year-olds to 13.5% (95% CI: 7.9, 21.9) among 57-59-year-olds. The age group x LTSP interaction term was not significant, indicating associations between age group and HR-HPV prevalence were not significantly different by number of LTSP (p=0.27). Similarly, interaction terms in birth cohort-specific models were not significant (1950s: p=0.94, 1960s: p=0.87, 1970s: p=0.21). Negative associations between age and prevalence of varying magnitude and statistical significance were seen for all birth cohort and LTSP combinations (APC range: -13.11%, -4.37%).

Conclusions: While having a higher number of lifetime partners is associated with higher HR-HPV prevalence, in the United States, HR-HPV prevalence is negatively associated with age regardless of number of lifetime partners. These associations were seen in all birth cohorts, suggesting declines in HPV with age are not due to cohort effects.

#2314

2 - Epidemiology and natural history

AGE-SPECIFIC PREVALENCE OF HUMAN PAPILLOMAVIRUS AND ABNORMAL CYTOLOGY IN A DIVERSE STATEWIDE COHORT OF INDIVIDUALS UNDERGOING CERVICAL CANCER SCREENING IN MISSISSIPPI

Clarke M[1], Risley C[2], Stewart M[3], Geisinger K[4], Hiser L[5], Morgan J[6], Owens K[7], Ayyalasomayajula K[8], Rives R[9], Jannela A[10], Grunes D[11], Zhang L[12], Schiffman M[13], Wagner S[14], Boland J[15], Bass S[16], Wentzensen N[17]

[1]National Cancer Institute, NIH, Rockville, United States

[2]National Cancer Institute, NIH, Rockville, United States

[3]University of Mississippi Medical Center, Jackson, United States

[4]Joint Pathology Center, Silver Spring, United States

[5]University of Mississippi Medical Center, Jackson, United States

[6]University of Mississippi Medical Center, Jackson, United States

[7]University of Mississippi Medical Center, Jackson, United States

[8]University of Mississippi Medical Center, Jackson, United States

[9]University of Mississippi Medical Center, Jackson, United States

[10]University of Mississippi Medical Center, Jackson, United States

[11]University of Mississippi Medical Center, Jackson, United States

[12]Mississippi State Department of Health; University of Mississippi Medical Center, Jackson, United States

[13]National Cancer Institute, NIH, Rockville, United States

[14]National Cancer Institute, NIH, Rockville, United States

[15]National Cancer Institute, NIH, Rockville, United States

[16]National Cancer Institute, NIH, Rockville, United States

[17]National Cancer Institute, NIH, Rockville, United States

Background/Objectives: In the U.S.,Mississippi (MS) ranks among the highest with respect to cervical cancer incidence and mortality, with persistently higher rates observed among Blacks compared to Whites. The current study evaluates the age- and race-specific prevalence of high-risk human papillomavirus (HPV) infection and abnormal cytology in a statewide cohort of individuals attending cervical screening in MS.

Methods: This study includes individuals aged 21 and older undergoing cervical cancer screening at the University of Mississippi Medical Center (UMMC) and the Mississippi State Department of Health (MSDH) with HPV testing data from 05/08/2018-11/26/2018. We calculated the proportion of HPV positivity, overall and by HPV16/18 versus other high-risk 12 types, as well as the proportion of low-and high-grade cytology by race and stratified by five-year age groups. We also analyzed age-specific HPV prevalence data from the National Health and Nutrition Examination Survey (NHANES, 2013-2016) by race.

Results: A total of 6,871 individuals (mean age of 35.7 years) were included. The prevalence of HPV was 25.6% and was higher in Blacks (28.0%) compared to Whites (22.4%). HPV prevalence was significantly higher in Blacks aged 21-24 years (50.2%) and 30-34 years (30.2%) compared to Whites in the same age groups (32.1% and 20.7%; $p<0.0001$, respectively). The prevalence of high-grade cytologic abnormalities, a cytologic sign of cervical precancer, peaked earlier Blacks (ages 25-29) compared to whites (35-39). We observed similar age- and race-specific HPV prevalence patterns in NHANES.

Conclusions: Blacks undergoing cervical cancer screening in MS have higher HPV prevalence at younger ages compared to Whites, particularly infections with other high-risk 12 HPV types. Blacks also experienced an earlier peak of high-grade cytologic abnormalities compared to Whites. These findings may have implications for natural history modeling, risk estimation, and recommendations for HPV-based screening. Studies of cervical carcinogenesis and screening are scarce in diverse, underserved populations like MS. STRIDES is addressing this critical gap and will make important contributions to understanding HPV natural history and cervical precancer risk in a diverse high-risk population.

#2224

8 - HPV testing

HPV73 in cervical cancer and distribution of HPV73 variants in cervical dysplasia

Forslund O[1], Söderlund-strand A[2], Darlin Flygh L[3], Borgfeldt C[4]

[1]LUND UNIVERSITY, Lund, Sweden

[2]Lund University, Lund, Sweden

[3]Lund University, Lund, Sweden

[4]SKANE UNIVERSITY HOSPITAL, LUND UNIVERSITY, Kristianstad, Sweden

Background/Objectives: HPV73 is classified as possibly oncogenic and is not recognised by most commercial primary HPV screening platforms. The aim was to determine the prevalence of HPV73 among invasive cervical cancers, formalin fixed paraffin embedded (FFPE) samples (N=69), from southern Sweden during 2009-2010. Another aim was to determine proportions of HPV73 among Aptima HPV assay negative cervical cancers (N=13, out of 181 cancers), and of high grade cytological cervical diagnosis (N=75, out of 5808 high grade lesions of ASC-H, HSIL, or suspected SCC) among liquid based cytology (LBC) samples collected between 2016-2019. We also investigated the distribution of HPV73 variants A1, A2 and B among HPV73-positive cases.

Methods: HPV73 was detected by multiplex MGP-PCR and Luminex, and HPV73 variants were identified by sequencing PCR amplicons.

Results: HPV73 was detected in 2.9% (2/69, 95% CI: 0.18-9.9) of the FFPE cervical cancer series. Among the Aptima HPV negative LBC samples, HPV73 was present in 38.5% (5/13) of the cancers and 29.3% (22/75) of the different high grades of cervical diagnosis. The A1, A2 and B variants were present in 6.9% (2/29), 82.7% (24/29) and 10.3% (3/29) of the HPV73-positive women, respectively. Among the seven HPV73 cancer cases (two FFPE- and five LBC-samples), six A2 and one A1 isolate were detected.

Conclusions: The observed prevalence of HPV73 (2.8%) in cervical cancers and its relative high occurrence (38%) among Aptima HPV-negative cancers urge that detection of HPV73 should be included in future primary HPV screening programs. Overall, the A2 variant of HPV73 was most common in our region.

#2294

2 - Epidemiology and natural history

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

Del Pino M[1], Vorsters A[2], Joura E[3], Doorbar J[4], Haniszewski M[5], Asensio Gudina I[6], Kodjamanova P[7], Velicer C[8], Drury R[9]

[1]HOSPITAL CLINIC DE BARCELONA, Barcelona, Spain

[2]UNIVERSITY OF ANTWERPEN, Antwerp (wlirijk), Belgium

[3]Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria

[4]University of Cambridge, Cambridge, United Kingdom

[5]Amaris Consulting, Toronto, Canada

[6]Amaris Consulting, Barcelona, Spain

[7]Amaris Consulting, Sofia, Bulgaria

[8]MERCK & CO., Kenilworth, Nj, United Kingdom

[9]MSD FRANCE, Lyon, France

Background/Objectives: Although adolescents are the primary cohort for routine HPV vaccination, adults not vaccinated earlier may still benefit from vaccination. However, vaccination of adults has lagged. Lack of consensus about which adults to target for vaccination and reimbursement barriers have likely contributed to this missed prevention opportunity. To help guide policy development, clinical decision-making, and further research, we summarized existing literature on risk factors for HPV infection and disease.

Methods: We searched MEDLINE, MEDLINE-IN-PROCESS and EMBASE for observational studies published in English between 2009 and 2020 that reported relative risks (RRs) or odds ratios (ORs) for factors associated HPV infection or disease in adults. Level of evidence of association was qualitatively assessed (weak, moderate, strong), using pre-determined criteria (e.g., magnitude of adjusted ORs/RRs).

Results: We identified 153 studies meeting selection criteria. Studies were geographically diverse. Most (60%) had >500 subjects; 35% had 100-500 subjects. HIV+ was strongly associated with infection; some studies reported >10-fold increased risk among HIV+ women and men who have sex with men (MSM). Other factors with strong associations included number of sex partners, history of genital warts (GW), sexually transmitted infection (STI) (up to 4-fold increase), oral contraceptive use (up to 6-fold increase), inconsistent condom use (up to 2-fold increase), no prior pregnancy/childbirth (up to 5-fold increase), and lupus diagnosis. Inverse associations with age were often found in women but not men. Marital status of women was inconsistently associated with infection. Factors associated with oral infection may include oral hygiene and sexual orientation (lesbian, bisexual female) but data were limited. Factors associated with disease were less commonly reported but included history of GW and smoking.

Conclusions: Despite differences in study design and inconsistent reporting of risk factors that limited comparisons across studies, our review confirmed some risk groups and risk factors widely believed to be associated with adult infection (e.g., HIV+, number of sex partners, MSM). The inconsistent association found between marital status and infection may be particularly notable, since providers may assume their married patients are not at risk. Other potential risk factors for infection (e.g., poor oral hygiene, lesbian/bisexual orientation for women), risk factors for men across adulthood, and risk factors for disease, require more investigation and confirmation. Further research could help guide policymaking and clinical decision-making for adult HPV vaccination.

#2236

8 - HPV testing

Clearance of HPV after Conization of Cervical Cancer and Adenocarcinoma in Situ Correlates with Absence of Cancer

Siegler E[1], Goldberg Y[2], Siegler Y[3], Shaked-mishan P[4], Mazareb S[5], Sabu E[6], Kugelman N[7], Mackuli L[8], Lavie O[9], Segev Y[10]

[1]Carmel Medical Center, Haifa, Israel
[2]Carmel Medical Center, Haifa, Israel
[3]Rambam Medical Centerr, Haifa, Israel
[4]Carmel Medical Center, Haifa, Israel
[5]Carmel Medical Center, Haifa, Israel
[6]Carmel Medical Center, Haifa, Israel
[7]Carmel Medical Center, Haifa, Israel
[8]Carmel Medical Center, Haifa, Israel
[9]Carmel Medical Center, Haifa, Israel
[10]Carmel Medical Center, Haifa, Israel

Background/Objectives: To examine thr correlation of clearence of High -Risk Human Papiloma Virus (HR-HPV) after Large Loop Excision of Transformation Zone (LLETZ) with absence of residual disease, in women diagnosed with cervical cancer and Adenocarcinoma in situ (AIS) .

Methods: Data were collected from 92 women diagnosed with cervical cancer and AIS who were positive to HR-HPV, and had a repeat cervical HPV test 3-12 weeks post-LLETZ, and before final surgical treatment. We compared characteristics of women with negative and positive HR-HPV post-LLETZ.

Results: The pathological results of women who were HR-HPV negative (n=40) compared to HR-HPV positive (n=52) at the post-LLETZ follow-up visit included a significantly higher incidence of adenocarcinoma: 17 (42.5%) vs 5 (9.6%), (p=0.0007); a higher incidence of AIS; and a higher proportion with early stage cervical cancer. In the negative HR-HPV post-LLETZ group, 36 (90%) had normal histology and only 2 (5%) had cancer in the final histological specimen. Among women who underwent radical hysterectomy/trachelectomy after LLETZ, a normal final histology was observed in 75% and 9% of those who were HR-HPV negative and HR-HPV positive, respectively (p<0.0005). The negative predictive value for residual cancer, with clearance of HR-HPV after LLETZ was 95%.

Conclusions: Clearance of HR-HPV from the cervix a short time after LLETZ has a high correlation with the absence of residual cancer in the final outcome, either in the pathology or the follow up. Testing for HR-HPV a short time after LLETZ might serve as a parameter for risk assessment.

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#2159

9 - HPV screening

PREVALENCE OF GENITAL HPV-INFECTIONS AMONG FEMALE TRANSPLANT RECIPIENTS

Hillen C[1], Sachs C[2], Jaeger A[3], Prieske K[4], Kaufmann A[5], Lütgehetmann M[6], Schmalfeldt B[7], Sterneck M[8], Woelber L[9]

[1]UNIVERSITY HOSPITAL HAMBURG EPPENDORF, Hamburg, Germany

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

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

[4]Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Mildred Scheel, Hamburg, Germany

[5]CLINIC FOR GYNECOLOGY, CHARITÉ-UNIVERSITAETSMEDIZIN BERLIN, Berlin, Germany

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

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

[8]Department of Hepatobiliary and Transplant Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, Hamburg, Germany

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

Background/Objectives: Immunosuppressive therapy used to prevent rejection in transplant recipients is associated with a higher risk of developing anogenital (pre)malignancies related to HPV-infections. Previous studies regarding the prevalence of high risk (hr)HPV-infection among female transplant recipients have been contradictory. Larger studies with accurate patient assessment are needed to evaluate hrHPV prevalence in this risk group compared to the hrHPV prevalence of >30-year-old women in the general population (4-6%).

Methods: Women who had undergone a kidney or liver transplant at least one year ago received HPV testing of the uterine cervix with Cobas® HPV Test (Roche Diagnostics). If tested positive, further genotyping was performed (AnyplexTM II HPV28 (Seegene)). All participants complete a questionnaire regarding medication, sexual behaviour, transplant history and medical history. The recruitment for the study is still ongoing.

Results: 144 patients at a median age of 52 years have been included in the study so far. 72 women had a history of kidney, 64 women of liver transplantation, and 8 women received simultaneous liver and kidney transplantation. Overall, the median duration of immunosuppressive therapy was 8 years (7 years in kidney transplant recipients and 9 years in liver transplant recipients). 132/144 (91.7%) women had attended cervical cancer screening with Pap smear at least once a year before inclusion in the study. HrHPV-testing of the uterine cervix was positive in 21/144 (14.6%) cases. 12/72 (16.7%) in kidney transplant recipients and 8/64 (12.5%) in liver transplant recipients. The most common type detected was hrHPV 16 9/21 (42.9%). The median number of sexual partners was 6 within the women tested HPV-positive versus 3 in the group tested negative (p=0.036). In 17 out of 144 cases, the women received an HPV vaccination in the past. There were 4 women tested positive for hrHPV within the vaccinated cohort. However, 3 of them were vaccinated after the first sexual intercourse.

Conclusions: Data indicate that cervical hrHPV-prevalence is more than doubled among female transplant recipients compared with the general population. While most women (92%) already participate in regular cervical cancer screening, additional colposcopy might be beneficial to screen for (pre)invasive lesions of the anogenital region in these patients.

#2392

2 - Epidemiology and natural history

Cytology and HPV Molecular epidemiology for 2362 women engaged in cervical cancer screening in French University Hospitals from 2016 to 2020

Abraham S[1], Ferré V[2], Bucau M[3], Ichou H[4], Collin G[5], Le Hingrat Q[6], Onambele M[7], Felce M[8], Luton D[9], Mandelbrot L[10], Chnecker C[11], Ceccaldi P[12], Biassette H[13], Auberger E[14], Davitian C[15], Descamps D[16], Couvelard A[17], Charpentier C[18]

[1]Service de Virologie, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[2]Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[3]Département de Pathologie, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[4]Service de Virologie, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[5]Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[6]Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[7]Service de Virologie, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[8]Département de Pathologie, AP-HP, Hôpital Beaujon, Paris, France

[9]Service de Gynécologie-Obstétrique, Université de Paris, INSERM U1016, Institut IMAGINE, AP-HP, Hôpit, Paris, France

[10]Service de Gynécologie-Obstétrique, Université de Paris, Inserm IAME 1137, AP-HP, Hôpital Louis Mouri, Paris, France

[11]Département de Pathologie, Université de Paris, AP-HP, Hôpital Lariboisière, Paris, France

[12]Service de Gynécologie-Obstétrique, Université de Paris, Laboratoire URB2i (UR 4462), AP-HP, Hôpital, Paris, France

[13]Département de Pathologie, Université de Paris, AP-HP, Hôpital Lariboisière, Paris, France

[14]Département de Pathologie, Groupement Hospitalier Eaubonne-Montmorency, Hôpital Simone Veil, Paris, France

[15]Service de Gynécologie-Obstétrique, AP-HP, Hôpital Beaujon, Paris, France

[16]UNIVERSITÉ DE PARIS, INSERM, , France

[17]Département de Pathologie, Université de Paris, INSERM U1149-CRI, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

[18]Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

Background/Objectives: In France, cervical cancer screening recommendations switched from primary cytology testing to primary HPV testing in mid-2020. This study aimed to describe high-risk HPV (hrHPV) prevalence according to cervical cytology among samples received for HPV testing before recommendations switch.

Methods: Cervical samples collected in 5 hospitals in Paris were first analyzed for cytology using Bethesda classification. All samples addressed based on abnormal cervical cytology or upon clinical specific request for HPV testing from January 2016 to May 2020 were analyzed with AnyplexIITM HPV28 (Seegene). For patients with multiple screenings, only the first cervical samples were retained. hrHPV were defined following IARC classification: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.

Results: HPV testing was performed on 2362 samples. Median age was 38 years-old (y) (IQR=31-47). 70.6% showed Atypical Squamous Cell of Unknowned Significance (ASC-US) cytology and 13.2% had lesions (Low Grade Squamous Intraepithelial Lesion (LSIL), High Grade Squamous Intraepithelial Lesion (HSIL), Atypical Squamous Cell evocating High grade lesion (ASC-H), Atypical Glandular Cells (AGC)). Overall, 42.8% of women harboured at least 1 hrHPV and the most prevalent were HPV16 (9.5%) followed by HPV52 (8.0%) and HPV31 (6.8%). HPV18 ranked seventh in terms of prevalence (4.5%). Overall, there was a single hrHPV in 26% of samples, two in 10.5%, three in 4.7% and at least 4 hrHPV in 1.7% of cases. Women between 30 and 60y harboring HPV16/18 had significantly more cervical lesions at cytological exam (9.2% HPV16/18 positive in normal cytology vs 38.5% for HSIL, p=0.0002 and 25.0% for LSIL, p=2.7.10-5). This was not significant for women with HSIL under 30y (1.7% vs 14.3%, p=0.2). Detection of other hrHPV types in addition to HPV16/18 enables to catch up more pre-cancerous lesions. Indeed, among women aged 30 to 60y, for HSIL, 80.8% were hrHPV positive vs 38.5% HPV16/18 positive (p=0.04) and for LSIL it was 63.6% vs 25.0% (p=0.005). In the same way, for women under 30y, 100% of HSIL were hrHPV positive vs only 14.3% HPV16/18 positive (p=0.005) and 67.9% vs 26.8% for LSIL (p=2.5.10-5). For women with normal cervical cytology, hrHPV was more frequently detected than HPV16/18 alone (27.0% vs 8.0%, p=4.10-13).

Conclusions: This study shows a high prevalence (42.8%) of hrHPV among samples sent for HPV testing, which is concordant to primary triage on cytology abnormalities. HPV16 being the most prevalent hrHPV detected (9.5%) is representative of HPV epidemiology in pre-cancerous and cancerous lesions. Further analyses involving HIV status are ongoing. Since this study is based on cytology triage, it might not reflect the exact HPV epidemiology. Prevalence of some hrHPV non HPV16/18 being superior to 5% highlights the importance of using all hrHPV detection test in cervical cancer screening.

Percentage of hrHPV positive women by age and cervical cytology following Bethesda classification

#1811

2 - Epidemiology and natural history

TREATED AND UNTREATED HUMAN PAPILLOMAVIRUS INFECTION IS ASSOCIATED WITH PRETERM DELIVERY AND NEONATAL MORTALITY - A SWEDISH POPULATION-BASED STUDY

Wiik J[1], Nilsson S[2], Kärrberg C[3], Strander B[4], Jacobsson B[5], Sengpiel V[6]

[1]DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, INSTITUTE OF CLINICAL SCIENCES, SAHLGRENSKA ACADEMY, UNIVERSITY OF GOTHENBURG, Gothenburg, Sweden

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

[3]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[4]UNIVERSITY OF GOTHENBURG, Gothenburg, Sweden

[5]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[6]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Background/Objectives: Treatment of cervical intraepithelial neoplasia (CIN) is associated with an increased risk of preterm delivery (PTD) although the exact pathomechanism is not yet understood. Women with untreated CIN also seem to have an increased risk of PTD. It is unclear whether this is attributable to human papillomavirus (HPV) infection or other factors. We aimed to investigate whether HPV infection in conjunction with pregnancy, as well as previous treatment for CIN, is associated with an increased risk of PTD and other adverse obstetric and neonatal outcomes.

Methods: This was a retrospective population-based register study of women with singleton deliveries registered in the Swedish Medical Birth Register 1999-2016 (n=1,044,023). Exposure groups were defined based on cervical HPV-tests, cytology and histology, as registered in the Swedish National Cervical Screening Registry. Women with a lifetime history of exclusively normal cytology (n=338,109) were compared to women with positive HPV-tests (n=2,550) or abnormal cytology (n=11,727), women treated for CIN3 (n=23,185) and with CIN2+ diagnosed after delivery (n=33,760). Exposure groups were compared by logistic regression and comparisons were adjusted for socioeconomic and health-related confounders.

Results: HPV infection was associated with PTD (odds ratio (OR) 1.19, 95% confidence interval 1.01-1.42), preterm prelabour rupture of membranes (pPROM) (OR 1.52, 1.18-1.96)), prelabour rupture of membranes PROM (OR 1.24, 1.08-1.42) and neonatal mortality (OR 2.69, 1.25 - 5.78)). Treatment for CIN was associated with PTD (OR 1.85, 1.76-1.95), spontaneous PTD (OR 2.06, 1.95-2.17), pPROM (OR 2.36, 2.19-2.54), PROM (OR 1.11, 1.05-1.17), intrauterine fetal death (OR 1.35, 1.05-1.72), chorioamnionitis (OR 2.75, 2.33-3.23), intrapartum fever (OR 1.24, 1.07-1.44), neonatal sepsis (OR 1.55, 1.37-1.75) and neonatal mortality (OR 1.79, 1.30-2.45). Women with CIN2+ diagnosed within three years after delivery had increased PTD risk (OR 1.18, 1.10-1.27).

Conclusions: Women with HPV infection have increased risk of PTD, pPROM, PROM and neonatal mortality. Treatment for CIN increases risks further and seems to confer a risk of maternal and neonatal infectious complications.

FC06 - Screening II

#2256

9 - HPV screening

INVESTIGATING LOSS TO FOLLOW-UP IN THE DUTCH CERVICAL CANCER SCREENING PROGRAMME

Olthof E[1], De Kok I[2], Van Kemenade F[3], Siebers A[4], Aitken C[5]

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

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

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

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

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

Background/Objectives: Loss to follow-up within cervical cancer (CC) screening programmes can lead to missing clinically relevant lesions and may impact on the effectiveness of organized programmes. The consequences of loss to follow-up within the screening programme on the risk of missing precancerous lesions is not regularly studied. This study had two aims. Firstly, to examine during which step most women are lost to follow-up in the referral pathway of the Dutch CC Screening Programme and to identify the demographic and screening characteristics of these women and secondly, to estimate the risk of precancerous lesions of these women, using data from women compliant with follow-up.

Methods: Data from the Dutch nationwide network and registry of histo- and cytopathology (PALGA) was used.Women screened within the primary hrHPV-based CC screening programme between 1 January 2017 and 31 March 2019 were included. Loss to follow-up in the referral pathway was quantified at each step in the programme pathway. Demographic and screening characteristics for women lost to follow-up were compared to women who were not lost to follow-up and were analyzed using logistic regression analysis. Potential CIN2+ and CIN3+ detection rates were calculated per loss to follow-up moment to estimate the risk of precancerous lesions by using a proxy of CIN risk in women not lost to follow-up.

Results: From the 868,295 screened women, most women were lost to follow-up after an advice for direct referral (1,262 (5.2%) for GP and 115 (8.0%) for self-sampling (ZAS)) and an advice for indirect referral to the gynecologist (1,244 (13.1%) for GP and 74 (19.0%) for ZAS), and after being triaged for repeat cytology after six months (2,687 (5.3%) for GP and 490 (18.8%) for ZAS). The highest risk on CIN3+ was found in women after direct (27.7%) and indirect (15.2%) referral to the gynecologist. The lowest risk on CIN3+ was found in women after an inadequate cytology after six months (1.5%) and in women being triaged for repeat cytology after six months (2.6%). Of all women that were lost to follow-up, the total number of potentially missed CIN2+ and CIN3+ was 1,289 (20.3%) and 718 (11.3%).

Conclusions: Within the screening programme, most women are lost to follow-up after referral to the gynecologist and after being triaged for repeat cytology after six months. The most clinical relevant lesions were potentially missed due to loss to follow-up after referral to the gynecologist. The existing gap between the screening programme and clinical care requires further attention. If loss to follow-up could be reduced, the effectiveness of the CC screening programme could be increased by 9.3%.

#2265

9 - HPV screening

HPV TESTING IN POLISH POPULATION-BASED CERVICAL CANCER SCREENING PROGRAM - INTERIM ANALYSIS OF A RANDOMISED HEALTH SERVICES STUDY

Nowakowski A[1], GliÅfska P[2], Macios A[3], Komerska K[4], Olkowicz J[5], Kaminski M[6]

[1]Department of Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[2]Department of Oncological Gastroenterology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[3]Department of Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[4]Department of Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[5]Department of Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

[6]Department of Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background/Objectives: To assess performance of High Risk Human Papillomavirus (HR HPV) testing with reflex liquid based cytology (LBC) and compare it to performance of current standard conventional cytology/LBC in cervical cancer screening in Poland.

Methods: An interim analysis of the HIPPO project (HPV Testing In Polish POpulation-based Cervical Cancer Screening Program) was performed. HIPPO is a randomized health services study nested in the Organized Cervical Cancer Screening Program (OCCSP) in Poland.The project assumes recruitment of 33,000 women aged 30-59 years attending OCCSP. Women (stratified by age) are randomized in a 1:1 ratio to cytology or HR HPV. HPV HR (+) women with ≤ ASC-US reflex LBC are referred for colposcopy in the molecular arm. In the cytology arm women with repeated ASC-US cytology and ≤ LSIL are referred for colposcopy. Primary end-points include detection rates of histologically confirmed high grade intraepithelial lesions or worse in each arm. This analysis was performed on data collected between October 2019 and September 2020 in Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw before expansion of the project to other sites in the country.

Results: Data on 1,213 HR HPV tests and 1,184 Pap smears were assessed. Referral rate to colposcopy in HR HPV and cytology arm was 4.37% and 2.79%, respectively (p-value 0.037). CIN2+ detection rate was higher in the HR HPV arm than in cytology arm (Intention-to-treat analysis: 1.07%; 95% CI: 0.51%-1.83% vs. 0.34%; 95%CI: 0.09%-0.86%, p-value 0.032).

Conclusions: An interim analysis of the HIPPO project revealed nearly 3-fold higher detection rate of CIN2+ and nearly 2 fold higher colposcopy referral rate in HR HPV-based screening compared to current standard of cytology. Results were analyzed by external Data Safety Monitoring Board and a positive recommendation for countrywide expansion of the project was given.

#2291

9 - HPV screening

Predictions in the results of the second hrHPV screening round given the changing landscape: A modelling study

Kaljouw S[1], Jansen E[2], Aitken C[3], De Kok I[4]

[1]ERASMUS MEDICAL CENTER , Delft, Netherlands

[2]Erasmus Medical Center, Rotterdam, Netherlands

[3]ERASMUS MC UNIVERSITY MEDICAL CENTER, Rotterdam, Netherlands

[4]ERASMUS MEDICAL CENTER, Rotterdam, Netherlands

Background/Objectives: The Dutch primary high-risk human papillomavirus (hrHPV) based screening programme starts the second screening round in 2022. In this second screening round, the landscape changes with a partly vaccinated population starting screening while a more sensitive test in the first screening round has changed the distribution of disease in the eligible population. Additionally, starting in the second screening round a ten-year screening interval will be used for women between 40 and 60 who received a negative test result in the previous round (screening at ages 40, 50, 60). We aimed to investigate how the results of the screening programme change in the second screening round. Moreover, we investigate how these results are influenced by changing the screening interval for women over 40 years old.

Methods: Microsimulation model MISCAN was used to simulate the Dutch population of women. For the years 2023-2026, we calculated the average cervical cancer incidence, number of primary hrHPV-tests, number of cytology tests, number of colposcopies and diagnoses as compared to the first screening round for the current programme. Additionally, we calculated these outcomes for two other screening strategies. We varied the screening interval between the ages of 40 to 60 for women with a negative test in the previous screening round: a five-year screening interval for users of the office-based test and the self-sampling kit (Self5GP5), and a five-year screening interval for users of the self-sampling kit and a ten-year interval for users of the office-based test (Self5GP10).

Results: With the current screening strategy, in the second screening round the number of primary tests, cytology tests and colposcopies decrease by 26%, 20% and 15%, respectively, compared to the first screening round. The number of false-positives decreases by 21% and the number of clinically relevant lesions decreases by 24% compared to the first screening round. In the strategy "Self5GP10' the number of false-positives decreased by 20% and the number of clinically relevant lesions decreased by 24% from the first to the second screening round. When comparing the first screening round and the second screening round for strategy "Self5GP5', we find that the number of false-positives and the number of clinically relevant lesions decrease by 5% and 14%, respectively.

Conclusions: We have shown that in the second screening round the number of tests and procedures change substantially compared to the first screening round. Although these differences are mainly caused by the 10-year screening interval for women over 40 years old, we also see a difference in these outcomes between the first and the second screening round for a screening interval with only 5 year intervals. It is important for healthcare professionals and policymakers to take this information into account.

#2301

9 - HPV screening

HPV BASED SCREENING STRATEGY IN YOUNGER WOMEN: A RANDOMIZED CONTROLLED TRIAL

Armaroli P[1], Rizzolo R[2], Gillio-tos A[3], De Marco L[4], Cristina S[5], Valentini S[6], Larato C[7], Giordano L[8], Ronco G[9]

[1]AOU CITTÀ DELLA SALUTE E DELLA SCIENZA, Turin, Italy

[2]CENTRE FOR CANCER PREVENTION, Turin, Italy

[3]Cancer Epidemiology Unit- C.E.R.M.S, Department of Medical Sciences, University of Turin, Turin, Italy

[4]CANCER EPIDEMIOLOGY UNIT- C.E.R.M.S, UNIVERSITY OF TURIN, , Italy

[5]Pathology Unit, S.S. Trinità Hospital ASL NO, Borgomanero, Italy

[6]Pathology Unit, S.S. Trinità Hospital ASL NO, Borgomanero, Italy

[7]Centre for Cancer Prevention,AOU Città della Salute e della Scienza, Turin, Italy

[8]Centre for Cancer Prevention,AOU Città della Salute e della Scienza, Turin, Italy

[9]INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, Torino, Italy

Background/Objectives: At younger age, with cytology-based screening, referral to colposcopy and overtreatment of regressive high-grade CIN and their impact on pregnancy outcomes are especially relevant while incidence of invasive cancer is low. HPV based screening without triage increases referral and possibly also overtreatment but both such increases seem minimal with triage. A very selective triage strategy, would be appropriate at this age and could even reduce referral and overtreatment compared to cytology-based screening. In particular, below age 30 HPV testing could in practice be used as a filter to select women who do not need screening up to 30. A randomised controlled trial was conducted to compare such a strategy with cytology-based screening

Methods: Women born in 1990-1992 (unvaccinated birth cohorts) invited for the 1st screening, or the 2nd round if the first had been performed with cytology and no CIN2+ found, within the organised screening programmes, Piedmont Region-Italy. The women providing informed consent were randomly assigned to: • Conventional arm: colposcopy if cytology >=ASC-US. New cytology at age 28 if negative. • Experimental arm: All women tested for HPV by Hybrid Capture 2. HPV- women referred for new HPV at age 30. HPV+ women reflex-tested for cytology and managed as in the cytology arm up to age 30. At age 30 more intensive triage will be applied. We report data at recruitment.

Results: Out of 18,953 women invited, 36.9% accepted and 5623 (80.3%) participated in the study. 2809 women were randomized to the experimental arm, 2814 to the conventional arm. In the experimental arm, 22.1% were HPV+. Among these women cytology was negative in 72.2%, 21.9% had an LSIL, 4.5% a HSIL+. 170 women were referred for colposcopy. In the conventional arm, 90.6% were negative, 4.9% had a LSIL, 1.3% a HSIL+. 234 women were referred for colposcopy. The recruitment data demonstrate a significant reduction in the immediate referral rate for colposcopy in the experimental arm (RR 0.73, 95%CI 0.59-0.89). No difference in CIN2+ DR between arms was observed (RR 1.06, 95%CI 0.51-2.25)

Conclusions: These preliminary data show a 27% reduction in referral for colposcopy, together with a similar CIN2+ DR in the two arms. This confirms the safety of the assessed strategy compared to the current practice. These results will be integrated with genotyping data and compared with the results of other studies aiming to define the most appropriate screening strategy in unvaccinated and vaccinated young women.

#2210

60 - Triage of HPV positive women

Introduction of p16/Ki67 dual stain cytology in a Danish routine screening laboratory: - lessons learned

Tranberg M[1], Gustafson L[2], Christensen P[3], Brøndum R[4], Andersen B[5], Andersen R[6], Hammer A[7]

[1]RANDERS REGIONAL HOSPITAL, Randers , Denmark

[2]1.Department of Public Health Programmes, Randers Regional Hospital, Denmark, 2. Department of Clinical Medicine, Aarhus Univers, Randers, Denmark

[3]Department of Pathology, Randers Regional Hospital, Randers, Denmark

[4]Department of Pathology, Randers Regional Hospital, Randers, Denmark

[5]AARHUS UNIVERSITY, Randers, Denmark

[6]Department of Pathology, Randers Regional Hospital, Randers, Denmark

[7]1. Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark, 2. Department of Clinical Medicine, Aarhus Univ, Aarhus, Denmark

Background/Objectives: Dual immunocytochemical staining for p16/Ki67 is a sensitive triage test in cervical cancer screening. Since dual staining is evaluator-dependent, sufficient training of novice evaluators may be critical to achieve safe implementation in routine laboratories and reduce the risk of misclassification. We aimed to determine the concordance in dual stain results between an expert in dual stain interpretation and novice evaluators, overall and stratified by the number of slides reviewed at three reading points.

Methods: The study was conducted at the Department of Pathology, Randers Regional Hospital, Denmark. Dual stain slides for this concordance analysis were selected from two ongoing studies evaluating the clinical accuracy of dual staining among women aged 45 and above. Dual staining was performed using the CINtec plus assay (Roche Diagnostics). Slides were randomly selected from three reading points at which novice evaluators had reviewed <30, ~300, and ≥500 dual stain slides, respectively. Concordance in dual stain results was assessed using Cohen's Kappa, κ.

Results: Of 600 eligible slides, 50 slides were selected for review as recommended by the manufacturer. Median age was 68 years (range: 58-74). Overall concordance was good (κ=0.68,95%CI: 0.60-0.76. Concordance enhanced with increasing number of slides reviewed at a given reading point, from moderate concordance (κ =0.47, 95% CI: 0.05-0.90) after reviewing <30 slides to good concordance (κ=0.66, 95% CI: 0.20-0.88) after reviewing ~300 slides and to very good concordance (κ= 0.88, 95% CI: 0.66-1.00) after reviewing ≥500 slides.

Conclusions: When reviewing p16/ki67 dual stain slides from older women, concordance increased when novice evaluators received more experience and additional training. While further evaluation is required, our results indicate that a significant amount of training and experience of novice evaluators may be mandatory to achieve accurate dual stain interpretation in this age group.

#2399

9 - HPV screening

THE POSSIBLE ROLE OF CYTOLOGY AND HR-HPV PARTIAL GENOTYPING AT 12-MONTH RECALL IN CERVICAL CANCER SCREENING WITH HR-HPV PRIMARY TEST

Pompeo G[1], Paganini I[2], Bisanzi S[3], Sani C[4], Mongia A[5], Burroni E[6], Filippo C[7]

[1]Regional Cancer Prevention Laboratory of ISPRO, Florence, Italy

[2]Regional Cancer Prevention Laboratory of ISPRO, Florence, Italy

[3]REGIONAL CANCER PREVENTION LABORATORY OF ISPRO, Florence, Italy

[4]REGIONAL CANCER PREVENTION LABORATORY OF ISPRO, , Italy

[5]General Laboratory of Careggi University Hospital, Florence, Italy

[6]ISPRO, Firenzei, Italy

[7]Regional Cancer Prevention Laboratory of ISPRO, Florence, Italy

Background/Objectives: In Tuscany region,according to the Italian guidelines,HR-HPV positive women that had a negative cytological triage are re-called after 12 months to repeat the HPV DNA test.Women are then referred to colposcopy,if persistent to HR-HPV(no triage tests: fig. 1).We registered an high persistence of HPV at 12-month recall,causing an overload of colposcopy services.The aim of this study is to evaluate an alternative protocol for managing persistent HPV positive women at 12-month recall in order to minimize unnecessary referral to colposcopy,in terms of reduction of colposcopy referral rate and possible loss of CIN2+ lesions.

Methods: This study analyses the results of women (enrolled in the Florentine area between 2013 and 2018) showing HR-HPV persistent infection at 12-month recall.We considered only HR-HPV positive women at the first screening episode.HR-HPV test was performed with two HR-HPV validated screening methods:HC2 HR-HPV test(until may 2016),replaced with Cobas 4800 HPV Test after public tender.Pap test slides were prepared with an automatic platform(ThinPrep 5000, Hologic), stained with Papanicloau method and interpreted using TBS 2014.

Results: 5565 women (86.8%) participated to the 12-months recall protocol;58.2% were HPV persistent and,of these,94.9% have done a colposcopic/histological exam.We found 356 cases of histological high-grade lesions or cancerous lesions:351 HSIL,one SCC and 4 ADK.With the actual protocol,the Detection Rate (DR) of HSIL+ histological lesions (CIN2+) and the positive predictive value (PPV) in the 12-months recall are,respectively,2.5‰ and 11.6%.We simulated to apply a semi-conservative protocol HPV+/cito+ to our data (fig. 2): it emerged that the HSIL+ histological lesions are more related to abnormal/inadequate cytology respect to NILM(26.2% vs 7.3%;p. <0.00001)and the 48.6% of women that had a HSIL+ histological lesion resulted NILM to 12-month recall.We simulated to apply also a protocol (fig. 3) that provides Cobas 4800 test partial genotyping and cytology in order to regain some HSIL+ histological lesions missed with cytology alone."HPV Other" types positive women were more related with a negative results of colposcopy/histology,respect to HPV16/18+ women (respectively 63.6% vs 52.7%;p<0.00001).With this alternative protocol,we would have identified immediately the 69% of HSIL+ histological lesions (46.8% HPV16/18+;22.2% HPV Other+/ASCUS+) and we would have avoided 59% of colposcopies.

Conclusions: These data suggest that it is safer to maintain the current Italian 12-month recall protocol (conservative protocol).We can hypothesize to apply semi-conservative protocol with genotyping+cytological triage (fig. 3) in those screening programs that regularly have an adhesion to colposcopy of 90-95% of invited women,allowing to recover the lesions not seen immediately in the next tests (6/12 months later). We are currently evaluating the correlation of "true HPV16/18+ persistence" and HSIL+ histological lesions.

#2401

9 - HPV screening

Registry-based assessment of diagnostic accuracy in cervical cancer screening in the Nordic countries

Partanen V[1], Anttila A[2], Heinävaara S[3], Lönnberg S[4]

[1]Finnish Cancer Registry, Helsinki, Finland

[2]FINNISH CANCER REGISTRY, Helsinki, Finland

[3]Finnish Cancer Registry, Helsinki, Finland

[4]Finnish Cancer Registry, Helsinki, Finland

Background/Objectives: HPV-based screening is becoming more prevalent in the Nordic cervical cancer screening programmes. It has been shown that HPV-based screening produces substantially more positive results compared to cytology-based screening. In most cases only the HPV test is positive, and no cervical abnormalities are found in reflex triage. The objective of the current study is to compare positive predictive values and detection rates between test methods and countries by combining screening test results with histopathological results from diagnostic colposcopies.

Methods: This study utilizes individual level data from Nordic population-based cervical cancer screening registers in Finland, Iceland, Norway and Sweden. Cervical test data from each country were converted to standard format and aggregated by calculating the number of test episodes for every test result for each calendar year and one-year age group and test method and linked to most severe histological results within 24 months of the test date.

Results: Positive predictive values and detection rates of precancerous cervical lesions or more severe findings will be reported.

Conclusions: Analysis of positive predictive values and detection rates provides between test methods and countries provides important insights on performance of screening. This information can be used in optimization and quality improvement of screening.

#2405

9 - HPV screening

EXPERIENCES OF THE FIRST YEAR OF ROUTINE COTESTING CYTOLOGY AND HPV IN GERMANY

Ikenberg H[1], Pittel B[2], Xhaja A[3]

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

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

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

Background/Objectives: Starting 1.1.2020 the German cervical cancer prevention program of the compulsory health insurance has shifted from annual cytology to HPV-cytology-cotesting every three years in primary screening for women >35 years. Cytomol is the largest lab for cervical cancer prevention in a single site in Europe. Here liquid based cytology (LBC, ThinPrep®, Hologic, Wiesbaden, Germany) with computer-assistance (IMAGER®, Hologic, Wiesbaden, Germany) has been offered as standard in cotesting since 2020 replacing conventional cytology with computer-assistance (FocalPoint®,B&D, Heidelberg, Germany).

Methods: Results of all cotesting cases from 1.1.2020-31.12.2020 with LBC and high-risk-HPV-DNA-testing (cobas®, Roche Diagnostics, Mannheim, Germany) are reported. Cytology findings are given according to the Munich nomenclature III as obligatory in Germany and translated as far as possible to TBS. Problems in the implementation phase are reported

Results: Alltogether 289.024 cases were analyzed. The percentage of HR-HPV positivity over all age groups was 6,26%. Ranging from 9,56% between 35 and 40 years to 3,26% over 70 years. The prevalence of HPV-16 was 22,9%. HPV-18 was found in 7,1% and the group of the other 12 HPV-HR types tested for in 78,8%. Multiple HPV types were detected in 8,5%. 0.61% of the tests were technically invalid. The cytology results were as follows: Pap 0 (TBS: unsatisfactory) 0,21%, Pap I and Pap II-a (NILM) 96,9%, Pap II-p/g (~ASC-US/AGC) 1,27%, Pap III p/g (~ASC-H/AGC) 0,17%, Pap III D1 (LSIL) 0,97%, Pap III D2 (HSIL) 0,24%, Pap IVa-p/g (HSIL) 0,12% and Pap V-p/g (carcinoma) 0,1%. The rates in the preceding year 2019 (without routine HPV testing) were higher for Pap II-p/g (1,66%) and lower for Pap III-p/g (0,13%), Pap III D1 (0,44%) and Pap IVa-p/g (0,04%). The rates of abnormal cytology findings decreased with age. The implementation of cotesting was stressed by several factors. The most serious challenges where the following: extreme late publication of rules and reimbursement (partially only 10 working days before start), lack of preparations from software providers, retroactive changes in access to and reimbursement of cotesting, wrong materials sent in regarding the right of cotesting, misinterpretation of guidelines regarding follow-up examinations, insufficient availability of expert colposcopy.

Conclusions: The start of cotesting was severely compromised by insufficient preparation by regulatory institutions, companies and doctor´s practices. However, the evaluation of the data from the first year in a large routine lab shows encouraging results. Clear trends to higher sensitivity and higher specificity were observed.

#2384

14 - Screening methods

Screening and vaccination: Results from Italian Study evaluating best strategies how to screen vaccinated women.

Carozzi F[1], Ronco G[2], Visioli C[3], Bisanzi S[4], Iossa A[5], Armaroli P[6], De Marco L[7], Rizzolo R[8], Venturino E[9], Del Mistro [10], Bonelli L[11], Giorgi Rossi P[12], Zappa M[13]

[1]Dept. Experimental and Clinical Biomedical SciencesUniversity of Florence, Florence, Italy

[2]INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, Torino, Italy

[3]ISPRO ONCOLOGICAL NETWORK, , Italy

[4]REGIONAL CANCER PREVENTION LABORATORY OF ISPRO, Florence, Italy

[5]ISPRO Oncological Network, Prevention and Research Institute, Florence, Italy

[6]AOU CITTÀ DELLA SALUTE E DELLA SCIENZA, Turin, Italy

[7]Center for Cervical Cancer Screening, City of Health and Science Hospital, Turin, Italy

[8]CENTRE FOR CANCER PREVENTION, Turin, Italy

[9]Pathological Anatomy Unit- San Paolo Hospital and Santa Corona Hospital, Savona, Italy

[10]ISTITUTO ONCOLOGICO VENETO, Padova, Italy

[11]Epidemiology Unit- Oncological Screening Coordination of the Liguria Region IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[12]AUSL-IRCCS DI REGGIO EMILIA, Reggio Emilia, Italy

[13]SC EPIDEMIOLOGIA CLINICA E DI SUPPORTO AL GOVERNO ISPRO, , Italy

Background/Objectives: The first women who were offered HPV vaccination in in Italy (in 2007/08) were born in 1992 and reached the age for cervical screening (25 years) in 2017. In 2018 the Ministry of Health promoted a project to define the best screening policies in girls vaccinated against HPV.

Methods: Women born in 1993-95 who participated in the Florence, Savona and Turin organized screening programs in 2019-20 and provided informed consent were enrolled and tested for HPV DNA. HPV negative women will be reinvited after 5 years. HPV positive women had reflex cytology. If it was ASCUS+ they were directly referred to colposcopy while WNL cytology will be repeated after 3 years. Screening and vaccine registries were linked locally. HPV tests were done by HC2 or Cobas. Positive cases were genotyped by the Anyplex II HPV HR Detection test (Seegene). The study was approved by Ethical Committees.

Results: The proportion of women registered as vaccinated increased from 48.8% in invited women to 58.25% in women participating to screening and 60.9% among the 10.062 enrolled women. In vaccinated vs. unvaccinated enrolled women HPV16 prevalence decreased by 98% (RR=0.02; IC95% 0.01-0.05) and HPV 18 by 94% (RR=0.06; IC95% 0.02-0.18). Types 31 and 45 also decreased significantly, the former by 74% (RR=0.26; IC95% 0.19-0.36) and the latter by 65% (RR=0.35; IC95% 0.22-0.57). HPV33 also decreased, although not significantly (RR=0.77; IC95% 0.53-1.10). A prevalence decrease of borderline significance of HPV51 was also observed in vaccinated women (RR=0.05; IC95% 0.69-1.05). The relative prevalence of women with infection by at least one of the remaining high-risk types was 0.99 (95% 0.90-1.09. In addition, no prevalence increase was observed in vaccinated women for any high-risk HPV type, i.e., there is no suggestion of type replacement. Overall, the HPV test positivity was 17% lower (RR=0.83; IC95% 0.77-0.90) in vaccinated versus unvaccinated women. Triage cytology was about 10% less frequently positive in vaccinated women, without reaching statistical significance (RR=0.91; IC95% 0.79-1.04). As a result, colposcopy referral was about 25% lower in vaccinated than in unvaccinated women (RR=0.75; IC95% 0.65-0.88). Some 0.56% of vaccinated women had a CIN2+ detected and 0.24% a CIN3 vs. 0.96% and 0.46% respectively of the unvaccinated. Thus, the risk of CIN2+ was reduced by 42% and that of CIN3+ by 46%. No CIN2+ with HPV16/18 infection was observed in vaccinated women. Lesions with HPV 31/33/45 infection were reduced by 68% (RR=0.32; IC95% 0.13-0.80).

Conclusions: A significant decrease in positivity to HPV testing was observed in vaccinated women, with protection almost complete for 16/18 infections and relevant for HPV31/33/35. The very similar occurrence of the remaining high-risk HPV types by vaccination status suggests little or no confounding in such estimates. Colposcopy referral and CIN2+ detection were also strongly reduced in vaccinated women, plausibly due to reduced infection but also to high propensity to participation in screening. This is, therefore, a low risk population needing low-intensity screening. On the basis of this study and of a literature review, in Italy start of screening will be delayed to 30 years in vaccinated women while active policies are needed for the high-risk unvaccinated population. Each region, before starting with the new protocol, must evaluate the quality of the intersection between screening and vaccination records.

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#1868

5 - HPV prophylactic vaccines

OUTCOME OF FIRST CERVICAL SCREENING ROUND AFTER SPONTANEOUS VACCINATION AGAINST HPV: AN ITALIAN COHORT STUDY

Del Mistro [1], Battagello J[2], Weis L[3], Gori S[4], Frayle H[5], Zappa M[6], Zorzi M[7], Consensus Study Working Group .[8]

[1]ISTITUTO ONCOLOGICO VENETO, Padova, Italy

[2]Veneto Tumour Registry, Azienda Zero, Padua, Italy

[3]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

[4]VENETO INSTITUTE OF ONCOLOGY IOV-IRCCS, Padova, Italy

[5]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

[6]SC EPIDEMIOLOGIA CLINICA E DI SUPPORTO AL GOVERNO ISPRO, , Italy

[7]VENETO TUMOUR REGISTRY, AZIENDA ZERO, , Italy

[8]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background/Objectives: A survey among girls/women of birth cohorts not included in active vaccination campaigns, living in the Veneto region (North-East of Italy), was conducted to investigate the frequency of spontaneous HPV vaccination and the outcomes of the first cervical cancer screening round in vaccinated girls, in comparison to non-vaccinated mates.

Methods: Women born between 1986 and 1992 and living in five Local Health Units were included. The frequency of spontaneous vaccination performed at 15-25 years of age (at least one dose of 4-valent or 9-valent HPV vaccine during 2008 and 2017 included) was calculated, overall and by birth cohort. Outcomes (compliance to invitation, primary test result, high-grade lesions detection) of the first test within the local organized, population-based screening (at 24-27 years of age) were compared for vaccinated and unvaccinated women. Differences in outcomes distribution among cohorts were tested using the chi-square test ($\chi 2$) and the Fisher's exact test in case of small sample size.

Results: Overall, 96,230 women were included; 4,718 (4.9%) HPV-vaccinated and 91,512 unvaccinated. The frequency of vaccination increased by birth cohort, ranging between 1.8% and 9.8% for girls born in 1986 and 1992, respectively. Vaccination was mostly performed after 17 years of age (88.1%), but age at vaccination decreased progressively by birth cohort ($p<0.0001$). The first invitation to screening was according either to the cytology (84.2%) or to the HPV (15.8%) protocol. Overall compliance was 60.8% among vaccinated and 56.6% among unvaccinated women ($p<0.0001$). Statistically significant differences were observed for both protocols. No difference in cytology positivity at the ASC-US threshold was recorded between vaccinated and unvaccinated women; HPV positivity was non-significantly lower ($p=0.54$) among vaccinated (17.3%) than unvaccinated women (18.8%). Detection rates (DR) for high-grade lesions were lower among vaccinated than unvaccinated women (0.8% vs. 1.2%, respectively, for CIN2+, with $p=0.08$; 0.0% vs 0.8% for cancer). The DR of CIN2+ increased with the age at vaccination, scoring respectively 0.0%, 0.5% and 1.4% for women vaccinated when they were 15-16, 17-20, and 21-25 years old ($p=0.02$).

Conclusions: In the Veneto region, spontaneous vaccination against HPV among 15-25 years old females has been increasing in frequency over time, with a progressive decrease of age at vaccination. In comparison to unvaccinated women, higher compliance to cervical cancer screening invitation and lower CIN2+ detection rate of vaccinated women was observed. The DR was directly correlated to the age at vaccination.

FC07 - Self-Sampling

#2212

10 - Self-sampling

Urine HPV-DNA detection for cervical cancer screening - analytical comparison of two HPV assays

Tranberg M[1], Jensen J[2], Bech B[3], Andersen B[4]

[1]RANDERS REGIONAL HOSPITAL, Randers , Denmark

[2]Denmark Research Unit for Reproductive Microbiology, Copenhagen, Denmark

[3]Research Unit for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

[4]AARHUS UNIVERSITY, Randers, Denmark

Background/Objectives: Urine collection for high-risk human papillomavirus detection (HPV) provides a potential alternative to physician-collected or vaginal self-samples for cervical cancer screening. Using two HPV DNA assays, we studied the concordance of HPV positivity in urine samples in comparison with vaginal self-samples and cervical cytology samples taken by the general practitioner (GP). We also assessed women's acceptance of urine collection and preferences towards the different sampling procedures.

Methods: One hundred fifty paired self-collected urine and vaginal samples and GP-collected cervical cytology samples were available from 30 to 59-year-old women diagnosed with ASC-US in the Danish cervical cancer screening program. After undergoing cervical sampling at the GP, the women collected first-void urine and vaginal samples at home and completed a questionnaire. Each sample was tested for HPV DNA using the GENOMICA CLART® and COBAS® 4800 assays. Concordance in HPV detection between sample types was assessed using Cohen's Kappa, κ. Sensitivity and specificity of HPV detection in urine were calculated using cervical sampling as reference.

Results: With the COBAS assay, urine showed good concordance to the vaginal (k=0.66) self-samples and cervical samples (k =0.66) for HPV detection. The corresponding concordance was moderate (k=0.59 and k=0.47) using CLART. Compared to cervical samples, urinary HPV detection had a sensitivity of 63.9% and a specificity of 96.5% using COBAS; compared with 51.6% and 92.4% for CLART. Invalid HPV test rates were 1.8% for COBAS and 26.9% for CLART. Urine collection was well-accepted and 42.3% of the women ranked it as the most preferred future screening procedure.

Conclusions: Home-based urine collection was well-accepted and ranked as the most preferred future screening procedure. The COBAS assay performed better than CLART with respect to higher HPV concordance between urine and both vaginal self-sampling and cervical sampling as well as fewer invalid HPV test results. Urinary HPV DNA detection with COBAS is feasible, but its accuracy may need to be improved before urine collection can be offered to non-attendees reluctant to both cervical sampling and vaginal self-sampling.

#2227

10 - Self-sampling

DETECTION OF HPV-SPECIFIC ANTIBODIES IN FIRST-VOID URINE OF WOMEN VACCINATED WITH A NONAVALENT HPV VACCINE

Téblick L[1], Pattyn J[2], Van Keer S[3], De Smet A[4], De Smedt P[5], Tjalma W[6], Panicker G[7], Unger E[8], Van Damme P[9], Vorsters A[10]

[1]Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, Antwerp, Belgium

[2]Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, Antwerp, Belgium

[3]UNIVERSITY OF ANTWERP, Antwerp, Belgium

[4]UNIVERSITY OF ANTWERP, Antwerp, Belgium

[5]Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, Antwerp, Belgium

[6]Multidisciplinary Breast Clinic, Gynaecological Oncology Unit, Department of Obstetrics and Gynaecology, Antwerp University Hosp, Antwerp, Belgium

[7]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for, Atlanta, United States

[8]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for, Atlanta, United States

[9]Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, Antwerp, Belgium

[10]UNIVERSITY OF ANTWERPEN, Antwerp (wlirijk), Belgium

Background/Objectives: Vaccine-induced HPV antibodies enter female genital secretions through transudation from the blood circulation and are detectable. The initial stream of urine, defined as first-void (FV) urine, washes away secretions that accumulate between the small labia and urethral opening. Our team provided the first proof that vaccine-induced HPV-specific antibodies (HPV-Abs) are detectable in FV urine of young (HPV vaccinated) women. Previous results showed significant correlations between vaccine-induced HPV-Abs detected in FV urine and paired serum samples. The aim of this study is to further assess if FV urine is a suitable non-invasive tool to monitor HPV-Abs.

Methods: For this study, 63 women (21-46 years old) participating in a clinical trial receiving three doses of a nonavalent HPV vaccine (EudraCT: 2015-005093-38) additionally provided a FV urine sample prior to vaccination and 7 months post first vaccination (serum data not available). After Amicon filtration and concentration, HPV-Ab concentrations were measured using M9ELISA, a multiplex direct virus-like particle (VLP) ELISA for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 IgG antibodies using the MSD detection platform. In addition, total IgG (BioPlex Pro Human Isotyping Assay), total protein (Pierce BCA Protein Assay Kit), human DNA and HPV DNA (Cobas 6800) concentrations were measured to study possible normalisation parameters.

Results: Results show excellent classifications of vaccinated vs. non-vaccinated samples (≥ 93.65%). In addition, ROC analyses showed high sensitivities for all included HPV types; ≥ 93.65%. Specificity results were promising as well; ≥ 92.06%. At both FV urine sampling time points, 11.1% (7/63) of the women were high-risk HPV DNA positive and five women (7.9%) had a persistent HPV infection. In two participants, HPV DNA was no longer detected and two new HPV DNA infections were recorded at the second time point. Correlations between HPV-Ab responses and additionally measured parameters were calculated and provided a first view towards normalisation possibilities.

Conclusions: With this study we demonstrated the clear potential of FV urine sampling to facilitate monitoring vaccine-induced immunity against HPV. However, to confirm the feasibility of FV urine for vaccine-induced HPV antibody detection and non-inferiority toward serum sampling, comprehensive data of larger clinical trials, including paired serum and FV urine samples, and normalisation of Ab responses are required.

#2230

10 - Self-sampling

Workflow and Performance of CE Marked BD Onclarity Assay with Self-Collection on the BD Viper LT System

Vaughan L[1], Gregory S[2], Galbraith L[3], Zheng K[4], Phillips K[5], Burns N[6], Rous C[7], Shah M[8], Stonebraker E[9], Andrews J[10]

[1]BD INTEGRATED DIAGNOSTIC SOLUTIONS, Sparks Glencoe, United States

[2]BD Integrated Diagnostic Solutions, Sparks, United States

[3]BD Integrated Diagnostic Solutions, Sparks, United States

[4]BD Integrated Diagnostic Solutions, Sparks, United States

[5]BD Integrated Diagnostic Solutions, Sparks, United States

[6]BD Integrated Diagnostic Solutions, Sparks, United States

[7]BD Integrated Diagnostic Solutions, Sparks, United States

[8]BD Integrated Diagnostic Solutions, Sparks, United States

[9]BD Integrated Diagnostic Solutions, Sparks, United States

[10]BD Integrated Diagnostic Solutions, Sparks, United States

Background/Objectives: Randomized control trials, pilot implementation studies and meta-analyses over the last decade have confirmed that self-collected HPV specimens provide the same sensitivity as physician-collected samples (1-3) However, this has not resulted in regulatory approval for this sample type. Here, we report on the workflow and performance of three new sample collection devices (Rovers® Evalyn® or Viba® brushes and the Copan FLOQSwab®) for use with the CE marked BD OnclarityTM HPV Assay run on the BD ViperTM LT System.

Methods: Samples can be self-collected at home or in the clinic using the devices and transported dry to the laboratory for testing. All devices are processed using a standardized workflow where the only manual step is to remove brush heads (Rovers) or break off the scored swab shaft (Copan) and deposit the device heads in 3 mL of HPV diluent buffer. The tubes are sealed with custom elastomeric reclosing septum caps which allows the sample to be processed without user intervention using just 0.8 mL of lysate.

Results: Here we report that all three devices have similar performance and are stable when transported dry for 30 days at 2-30°C with up to 6 days exposure at 40°C (samples are also stable at -20°C for 30 days)

Conclusions: The new ability to use these devices with the BD OnclarityTM Assay offers a single automated workflow coupled with the flexibility to choose a device that meets a screening program's needs. We believe this is an important addition to cervical cancer screening, extending the ability to reached underserved women, especially critical in the current global pandemic.

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#2162

10 - Self-sampling

COCOSS-TRIAL: CONCURRENT COMPARISON OF SELF-SAMPLING DEVICES FOR HPV-DETECTION

Kampers J[1], Ertik F[2], Hülse F[3], Stolte C[4], Böhmer G[5], Hillemanns P[6], Jentschke M[7]

[1]Hannover Medical School, Hannover, Germany

[2]Hannover Medical School, Hannover, Germany

[3]Hannover Medical School, Hannover, Germany

[4]IZD Hannover, Hannover, Germany

[5]IZD HANNOVER, Hannover, Germany

[6]Hannover Medical School, Hannover, Germany

[7]HANNOVER MEDICAL SCHOOL, Hannover, Germany

Background/Objectives: High-risk human papillomavirus (hr-HPV) infection of the cervicovaginal tract is known to be the major cause of cervical cancer. Similar to various other countries, Germany introduced an organized combined screening including cytology and HPV testing in 2020. Participation rate is in need of improvement. Cervicovaginal self-sampling could be an option to increase the participation rate. Objective: Comparison of two dry vaginal self-sampling devices and a device for the self-collection of first-void urine in combination with a PCR-based hr-HPV Test to evaluate the clinical performance (sensitivity for high-grade CIN 2+) of these devices. A cervical smear taken by a clinician during colposcopy was used as reference for HPV testing.

Methods: This open prospective multicenter trial recruited patients with an age above 30 referred to the two participating colposcopy clinics (Hannover Medical School and IZD Hannover) with abnormal results from cervical cancer screening from 03/2020 to 09/2020. Exclusion criteria were pregnancy or women with hysterectomy in the past. The sample size was calculated to achieve a power of 80%. All patients received three CE-certified self-sampling devices (FLOQSwabs, COPAN, Italy; Evalyn Brush, Rovers Medical Devices, the Netherlands; Colli-Pee, Novosanis, Wijnegem, Belgium) with instructions to read and apply at home in a pre-specified alternating order without medical assistance. HPV testing was performed after adequate preservation and DNA extraction. Histologal results from colposcopy or cervical excitional surgery after self-sampling were used as gold-standard.

Results: The data of 66 patients was analyzed. All carcinomas and over 95% of the CIN 3 lesions were found to be hr-HPV positive with all self-collection devices. In detail, the hr-HPV positivity rate for clinician sampling, ColliPee, FLOQSwabs and Evalyn Brush was 85,7%, 60,7%, 75% and 82,1% for CIN 2 (n= 28) and 91,6%, 95,8%, 95,8% and 95,8% for CIN 3 (n= 24).

Conclusions: Hr-HPV testing of self-collected first-void urine and dry vaginal self-samples showed a high sensitivity for CIN 3+ comparable to that of a clinician-taken smear.

#2383

10 - Self-sampling

Performance of 6 methylation markers tested on self-collected urine samples - feasibility study

Hippe J[1], Kampers J[2], Ertik F[3], Hülse F[4], Böhmer G[5], Stolte C[6], Jentschke M[7], Schmitz M[8], Hansel A[9]

[1]oncgnostics GmbH, Jena, Germany

[2]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

[3]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

[4]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

[5]IZD HANNOVER, Hannover, Germany

[6]IZD Hannover, Hannover, Germany

[7]Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

[8]ONCGNOSTICS GMBH, Jena, Germany

[9]ONCGNOSTICS GMBH, Jena, Germany

Background/Objectives: In high-income countries, a high proportion of cervical cancer is diagnosed in the population of screening non-attendees. To improve participation, one approach is to offer self-sampling in the screening for HPV-testing. Studies proved that HPV-based screening for cervical cancer is superior to cytology-based screening in preventing women from invasive cervical cancer regarding its sensitivity. To overcome the rather low specificity of HPV testing, triage tests, e.g. based on DNA methylation markers may be used. Aim of this feasibility study is to determine the performance of 6 methylation markers, comprising the diagnostic assay GynTect®, on self-collected urine samples in comparison to clinician taken samples.

Methods: 70 women scheduled for conization were asked to collect a urine sample using the Colli-Pee 20mL device from Novosanis (Belgium), prior to visiting two colposcopy clinics (Department of Gynaecology and Obstetrics, Hannover Medical School and IZD Hannover). Before conization, a clinician-taken cervical smear was collected for HPV and methylation marker analyses.

Results: The overall concordance for HPV testing from urine and cervical smear was quite high, and clinician-taken cervical smears were not superior compared to self-collected urine using Colli-Pee.

Conclusions: Methylation analyses on both sample collections are not yet completed. Results will be presented at the congress.

#2390

10 - Self-sampling

Preferences and Experiences Regarding the Use of the Self-Sampling Device in the hrHPV Screening for Cervical Cancer

De Waard J[1], Dieleman M[2], Wisman B[3], Schuuring E[4], Esajas M[5], Vermeulen K[6], De Bock T[7]

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

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

[3]UNIVERSITY MEDICAL CENTER GRONBINGEN, Groningen, Netherlands

[4]UNIVERSITY MEDICAL CENTER GRONINGEN, , Netherlands

[5]Department of Obstetrics and Gynaecology, University Medical Centre Groningen , Groningen, Netherlands

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

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

Background/Objectives: Background: To improve participation in the Dutch cervical cancer screening, a self-sampling device (SSD) has been introduced in 2017 into the Dutch population-based screening programme (PBS) for the early detection of cervical cancer. The aim of this study was to gather potential preferences and experiences that might influence a woman's decision to use the SSD in the Dutch PBS.

Methods: Methods: A systematic literature research was performed in the PubMed database. Studies that assessed preferences and experiences of women regarding the SSD were included, and preferences and experiences were extracted. In addition, in a qualitative study, the list of potential preferences and experiences specific for the Dutch PBS was extended based on semi-structured interviews with SSD-users as well as not-SSD-users who recently participated in the PBS.

Results: Results: Seventy-six studies were included in the literature research and sixteen interviews were performed. Frequently mentioned preferences and experiences for (not) using the SSD, in both the interviews and the literature were: practicality, comfort, fear of not performing the SSD procedure correctly, and doubts on whether the results of the high-risk human papillomavirus (hrHPV) test will be reliable. New preferences and experiences elicited in the interviews were: accessibility, not being aware the SSD was an option and the inconvenience that after an hrHPV-positive test result of the SSD, an additional smear test at the GP is necessary.

Conclusions: Conclusion: Several preferences and experiences play a role in the choice whether or not to use the SSD. Based on the currently found preferences and experiences, an app will be developed in order to assess which of these are the most important for women participating in the Dutch population-based cervical screening program. This study was supported by a ZonMw grant.

FC08 - Methylation

#2317

17 - Methylation

Preventing overtreatment of CIN2/3 lesions: the role of methylation markers in predicting (non-)regression. Results of the CONCERVE study.

Dick S[1], Kremer W[2], Heideman D[3], Steenbergen R[4], Bleeker M[5], Verhoeve H[6], Baal, Van M[7], Meijer C[8], Kenter G[9], Berkhof H[10]

[1]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

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

[3]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[4], Amsterdam, Netherlands

[5]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

[6]OLVG, Obstetrics and Gynaecology, Amsterdam, Netherlands

[7]Flevoziekenhuis, Obstetrics and Gynaecology, Almere, Netherlands

[8]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Leiden, Netherlands

[9]Amsterdam UMC, Vrije Universiteit Amsterdam, Obstetrics and Gynaecology, Amsterdam, Netherlands

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

Background/Objectives: The aim of population based screening is to detect and treat precursor lesions (CIN2/3) of cervical cancer. Currently the majority of these precursor lesions are treated by LLETZ, resulting in considerable overtreatment since many lesions show spontaneous regression. In the present study (CONCERVE) we have investigated whether the FAM19A4/miR124-2 test (QIAsure) can predict which CIN2/3 lesions show spontaneous regression.

Methods: Women with CIN2/3 lesions of whom the transformation zone was completely visible at colposcopy were prospectively followed for 24 months. Standard surgical excision was replaced by a wait-and-see policy. Every 6 months a cervical scrape was collected and a colposcopic examination was performed by a gynaecologist. HPV testing and FAM19A4/miR124-2 methylation were evaluated on all cervical scrapes. Regression was defined as no lesion or CIN1 and/or HPV negative with normal cytology and no evidence of CIN2+ during further follow-up. Increase in colposcopic volume of the lesion covering > 50% of the visible cervix or progression from CIN2 to CIN3 were indications for surgical intervention. Regression rates were estimated using the Kaplan-Meier method.

Results: In total, 114 women were included of whom 80 were diagnosed with CIN2 and 34 with CIN3. Mean age of women included was 31.2 years (range 20 to 53 years). At the end of the study, 39 of 114 women had received LLETZ, resulting in a reduction of 66% in surgical interventions. CIN2/3 lesions with a negative FAM19A4/miR124-2 result showed more regression (74.7%) compared with CIN2/3 lesions with a positive methylation result (51.4%) (p=0.013). Women with mild cytological abnormalities (ASC-US/LSIL) and a negative methylation result showed the highest regression rate (88.4%).

Conclusions: Women with CIN2/3 and a negative methylation test showed a very high rate of spontaneous regression. The highest regression rate was found in women with ASC-US/LSIL and a negative methylation result. Therefore, these women do not need to be referred for colposcopy for at least 2 years. The QIAsure methylation test as a triage test in HPV-positive women can reduce the colposcopy referral rate considerably. In addition, it can be used to set up an individual treatment modality for women with CIN2/3, whereby lesions with a high chance of spontaneous regression will not be treated.

#2246

17 - Methylation

Methylation analysis as a tool in cervical cancer screening

Lindroth Y[1], Borgfeldt C[2], Forslund O[3]

[1]DEPARTMENT OF LABORATORY MEDICIN, MEDICAL MICROBIOLOGY, LUND UNIVERSITY, , Lund, Sweden

[2]SKANE UNIVERSITY HOSPITAL, LUND UNIVERSITY, Kristianstad, Sweden

[3]Department of Laboratory Medicine, Medical Microbiology, Lund University, Lund, Sweden

Background/Objectives: In the region of Skåne, Sweden, primary HPV screening was implemented in 2017. Currently, cytology is used to triage HPV positive women. HPV positive women with abnormal cytology are referred for colposcopy, while HPV positive women with normal cytology will have a new HPV test after 3 years. We performed a pilot study,ï»¿ to investigate if a DNA methylation assay could be a useful tool in routine screening, as a complement to cytology.

Methods: We have performed methylation analyses on 62 liquid based cytology (LBC) samples from women subsequently diagnosed with cancer or CIN3. 17 samples from women later diagnosed with squamous cell carcinoma, 9 with adenocarcinoma, and 36 with CIN3 were analysed for DNA methylation of the human genes FAM19A4 and miR124-2 by use of the QIAsure kit. Most of these samples (n=51) had been assessed as normal cytology, whereas others (n=8) had been assessed as HSIL, and a small number as LSIL (n=3). The time between the cytology sample and the biopsy or cone that gave the histological diagnosis of cancer or CIN3, was in average 2.8 years (range 0.2-7.9 years). The average age of the women at the time of the cytology sample was 36.7 years (range 15-79 years).

Results: Methylation of FAM19A4 and/or miR124-2 was detected in all 7 abnormal cytology samples (2 classified as LSIL and 5 classified as HSIL) from women later diagnosed with squamous cell carcinoma. More interestingly, methylation was also detected in 5 of 10 seemingly normal cytology samples from women subsequently diagnosed with squamous cell carcinoma. 6 of 9 cytology samples diagnosed as normal, from women later diagnosed with adenocarcinoma, tested positive for methylation. Overall, for these 26 women, later diagnosed with cancer, metylation was found in the 18 cases (69%) wheras only 7 (27%) showed abnormal cytology. Cytology samples from women with later histological diagnosis of CIN3 showed methylation in 14 of 36 cases (39%). 11 of these 14 methylated samples were diagnosed as normal cytology.

Conclusions: Our results indicate that methylation can be detected in liquid cytology samples taken prior to the diagnoses of cancer and high grade lesions, also in cases where the cytology is normal. Methylation analysis has the potential to improve the cervix cancer screening. Additional work is in progress and will be presented at the conference.

#2245

17 - Methylation

Epigenome-wide DNA methylation signatures in cervical pre-invasive and invasive disease

Bowden S[1]

[1]Imperial College London, London, United Kingdom

Background/Objectives: Cervical cancer is one of the most prevalent and leading cause of cancer mortality for women worldwide. Persistent infection with HPV is associated with the development of cervical cancer. Although most infections are cleared by the immune response, the factors related to persistent infection and eventual carcinogenesis are less well understood. Epigenetic alterations have been shown to be essential in the development of many cancers; while aberrant hypermethylation of CpG sites has been associated with cervical carcinogenesis in several targeted studies, epigenome-wide exploration has been limited. In this epigenome-wide association study we explore differential DNA methylation signatures associated to CIN3 and cervical cancer, to better understand potential drivers and biomarkers of cervical carcinogenesis

Methods: After quality control, 247 samples of women attending gynaecological appointments, cervical screening and oncological treatment between 2014-2020 at an English and Greek referral hospital were obtained. Methylation signatures were obtained following bisulphite conversion of DNA extracted from exfoliated cervical cells and sequenced using the Illumina 850k array data. Principle component analysis and linear regression were used to identify associations between clinical variables to variance in the data. Generalized linear models (GLM) and a conditional logistic regression model (CLM) were used to test for association between CpG sites and case-control status. The normality of the p-values of GLM and CLM were assessed to adjust for appropriate confounding variables.

Results: Twelve clinical and technical variables showed significant association to the principle components of beta values. 33 CpG significantly associated to case control status ($p<5x10-6$) and had a mean methylation change of greater than 10% (delta beta>0.1) were identified (Figure 1). All 33 CpG sites showed gain of methylation.

Conclusions: This study highlighted the overall hypermethylation nature of cervical cancer as well as significant CpG sites strongly associated to cervical cancer. We also identified 33 CpG sites significantly associated to case status. Functional annotation suggested two CpG sites in ATX8NOS and ATP8A2 genes were of interest for future functional studies - these genes are currently known be involved in cervical cancer tumorigenesis. Methylation signatures of cervical cancer genes are promising for a diagnostic and prognostic tool.

#2243

17 - Methylation

Risk-stratification of HPV-positive women with low-grade cytology by FAM19A4/miR124-2 methylation and HPV genotyping

Dick S[1], Vink F[2], Berkhof J[3], Heideman D[4], Meijer C[5]

[1]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

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

[3]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[4]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[5]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Leiden, Netherlands

Background/Objectives: In the Netherlands,implementation of primary HPV screening with cytology triage has led to a two-fold increase in the number of colposcopy referrals. The increase is mainly caused by direct referral of HPV-positive women with borderline or mild dyskaryosis (BMD) cytology (comparable with ASC-US and LSIL). Further risk-stratification of HPV-positive women with BMD is warranted to improve the efficiency of HPV-based screening.

Methods: This study retrospectively evaluated the performance of FAM19A4/miR124-2 methylation analysis, HPV16/18 genotyping, HPV16/18/31/33/45 genotyping and combinations thereof in HPV-positive women with BMD (n= 294) from the Dutch VUSA-Screen and POBASCAM trials. Proportion of colposcopy referrals and CIN3+ risk within one screening round (i.e. up to 4 years) were calculated.

Results: Methylation analysis on samples with BMD cytology discriminated well, yielding a CIN3+ risk of 33.1% after a positive result and a CIN3+ risk of 9.8% after a negative result. The proportion of colposcopy referrals was 41.2%. HPV16/18 genotyping and HPV16/18/31/33/45 genotyping resulted in a 27.6% and 24.6% CIN3+ risk after a positive result, and a 13.2% and 9.1% CIN3+ risk after a negative result, respectively. HPV16/18 genotyping led to a referral proportion of 43.2% and HPV16/18/31/33/45 genotyping led to a referral proportion of 66.3%. The sensitivity of the triage strategies could be further enhanced by combining methylation and genotyping. The CIN3+ risk after a methylation- and HPV16/18/31/33/45-negative result was only 2.8% at the expense of a higher referral proportion of 75.5%.

Conclusions: The use of methylation analysis and/or HPV genotyping in HPV-positive women with BMD cytology can lead to a substantial reduction in the number of colposcopy referrals. The choice of the triage tests may vary across countries because they depend on local thresholds of colposcopy referral and CIN3+ risk.

#2217

17 - Methylation

HPV AND DNA METHYLATION TESTING IN URINE FOR CIN2/3 AND CERVICAL CANCER DETECTION

Van Den Helder R[1], Steenbergen R[2], Van Splunter A[3], Mom C[4], Martins I[5], Tjiong M[6], Rosier-van Dunné F[7], Van Der Avoort I[8], Bleeker M[9], Van Trommel N[10]

[1]Amsterdam University Medical Center (UMC), Vrije Universiteit Amsterdam, Department of Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

[2], Amsterdam, Netherlands

[3]Amsterdam University Medical Center (UMC), Vrije Universiteit Amsterdam, Department of Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

[4]Amsterdam UMC, Amsterdam Medical Center, Department of Gynecologic Oncology, Center of Gynecologic Oncology Amsterdam, Amsterdam, Netherlands

[5]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Epidemiology and Biostatistics, Amsterdam, Netherlands

[6]Amsterdam UMC, Amsterdam Medical Center, Department of Gynecologic Oncology, Center of Gynecologic Oncology Amsterdam, Amsterdam, Netherlands

[7]Tergooi, Department of Obstetrics and Gynecology, Blaricum, Netherlands

[8]Ikazia Ziekenhuis, Department of Obstetrics and Gynecology, Rotterdam, Netherlands

[9]Amsterdam University Medical Center (UMC), Vrije Universiteit Amsterdam, Department of Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands

[10]NETHERLANDS CANCER INSTITUTE, Amsterdam, Netherlands

Background/Objectives: Urine, as a liquid biopsy can be obtained easily, repeatedly, and noninvasively. The suitability of urine for the detection of cervical (pre)malignancies, relies both on shedding of cervical cells and on transrenal excretion of cell-free DNA into the urine [1,2]. Urine sampling offers an interesting solution in high-income countries to reach repetitive non-responders for cervical cancer screening as well as a solution to overcome the geographic and logistic burden for cervical cancer screening in low- and middle-income countries. We aimed to determine the performance of hrHPV and host cell gene DNA methylation analysis in urine for high-grade cervical intraepithelial neoplasia (CIN2 and CIN3) and cervical cancer detection. Paired cervicovaginal self-samples and cervical scrapes, currently used in cervical cancer screening, were tested for comparison.

Methods: In total, 275 women were included in this study. From 119 cervical cancer patients paired urine samples, cervicovaginal self-samples and cervical scrapes were collected. Urine samples and paired cervicovaginal self-samples were collected from 92 patients with a CIN2/3 lesion. Additionally, urine samples of age-matched healthy female controls were collected. Samples were tested for hrHPV DNA and five DNA methylation markers. Correlation of hrHPV DNA and DNA methylation markers within all three sample types was determined using Cohen's kappa statistics and the Spearman correlation coefficients and performance by logistic regression.

Results: A good concordance and correlation was found between hrHPV and methylation markers results amongst all three sample types of cervical cancer patients. Also in CIN2/3 patients, the molecular results obtained in urine and self-collected samples were highly correlated. Methylation levels were higher in urine from CIN2, CIN3 and cervical cancer patients compared to controls and increased with severity of disease.

Conclusions: For women currently unreached by conventional screening methods, hrHPV and DNA methylation analysis in urine offers a promising solution to detect CIN2/3 and cervical cancer.

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#2391

17 - Methylation

PAX1 and ZNF582 methylation analysis and improvement of cervical cancer screening

Wisman G[1], Li N[2], Hu Y[3], Liu Y[4], Zhang X[5], He Y[6], Van Der Zee A[7], Schuuring E[8]

[1]Gynecologic Oncology, Cancer Research Centre Groningen, University of Groningen, University Medical Centre Groningen, Groningen,, Groningen, Netherlands
[2]Gynecologic Oncology, Tianjin Central Hospital of Gynecology Obstetrics /Tianjin Key Laboratory of human development and reprodu, Tianijn, China
[3]Gynecologic Oncology, Tianjin Central Hospital of Gynecology Obstetrics /Tianjin Key Laboratory of human development and reprodu, Tianjin, China
[4]Pathology, Tianjin Central Hospital of Gynecology Obstetrics /Tianjin Key Laboratory of human development and reproductive regul, Tianjin, China
[5]Pathology, Tianjin Central Hospital of Gynecology Obstetrics /Tianjin Key Laboratory of human development and reproductive regul, Tianjin, China
[6]Gynecologic Oncology, Tianjin Central Hospital of Gynecology Obstetrics /Tianjin Key Laboratory of human development and reprodu, Tianjin, China
[7]Gynecologic Oncology, Cancer Research Centre Groningen, University of Groningen, University Medical Centre Groningen, Groningen,, Groningen, Netherlands
[8]Pathology, Cancer Research Centre Groningen, University of Groningen, University Medical Centre Groningen, Groningen, The Nether, Groningen, Netherlands

Background/Objectives: Cohorts of women with high-risk human papillomavirus (hrHPV) infection harbor a spectrum of cervical diseases, ranging from women with just transient hrHPV infections to patients with cervical cancer. In Asian populations previous studies showed that analysis of PAX1 and ZNF582 methylation status may help to better discriminate between the different cervical conditions. The current prospective study was designed to assess and compare the potential diagnostic role of PAX1 and ZNF582 methylation analysis in a Dutch and a Chinese cohort.

Methods: Methylation of PAX1 andZNF582 was evaluated in cervical scrapings from 2 independent patient groups. For the Dutch cohort, 190 scrapings with abnormal cytology (atypical squamous cells of undetermined significance (ASCUS) or worse), selected from the population-based screening program were included, of which 138 patients were hrHPV positive. For the hospital-based Chinese cohort, 246 liquid-based cytology samples were included of which 205 women with abnormal cytology (ASCUS or worse) and 227 women with hrHPV infection. PAX1 and ZNF582 methylation was detected using quantitative methylation-speciï¬c PCR (QMSP).

Results: PAX1 and ZNF582 methylation showed high and similar specificity of 91-97% for CIN2+ in both abnormal cytology as well as hrHPV-positive samples with moderate and similar sensitivity of 43-61% for CIN2+ in both cohorts. Sensitivity for CIN3+ improved to 55-86%, but with a lower specificity (85-93%). Sensitivity could be improved further with ~20% by combinations of PAX1 or ZNF582 with different previously identified CIN2+-specific methylation markers (ANKRD18P, C13ORF18, EPB41L3, JAM3, SOX1 and ZSCAN1).

Conclusions: The diagnostic performance of PAX1and ZNF582 methylation markers shows high specificity to detect CIN2+/CIN3+ lesions in scrapings with abnormal cytology or hrHPV-positivity irrespective of geography and race. These markers as triage test might significantly decrease the number of unnecessary colposcopies. Randomized controlled trials and further large prospective studies are needed to confirm our findings.

FC09 - Economics and Modelling

#2200

34 - Economics and modelling

THE PUBLIC HEALTH AND COST EFFECTIVENESS IMPACT OF 9VHPV VACCINATION ON ANAL AND PENILE CANCERS AMONG THE HIV-POSITIVE AND HIV-NEGATIVE MSM POPULATION IN GERMANY - PRELIMINARY RESULTS FROM A DYNAMIC TRANSMISSION MODEL

Palmer C[1], Stephan A[2], Wähner C[3], Reuschenbach M[4], Bauer A[5], Varga S[6], Kreuter A[7], Klussman J[8]

[1]Merck and Co., Inc., Kenilworth, Nj, United States

[2]MSD SHARP & DOHME GMBH, Haar, Germany

[3]MSD Sharp & Dohme GmbH, Haar, Germany

[4]MSD Sharp & Dohme GmbH, Haar, Germany

[5]MSD SHARP & DOHME GmbH, Haar, Germany

[6]MERCK AND CO., INC., Kenilworth, United States

[7]UNIVERSITY WITTEN/HERDECKE, , Germany

[8]Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty, University of Cologne, Cologne, Germany

Background/Objectives: Men who have sex with men (MSM) have significantly increased incidence of human papillomavirus (HPV) infection as well as related diseases. Although HPV vaccination for boys aged 9-14 (catch-up 15-17) has been recommended in 2018 and funded since 2019 in Germany, the MSM population above age 17 currently benefits little from the respective herd protection, therefore remaining a high-risk group. We estimated the cost-effectiveness and public health impact with regard HPV-related anogenital (anal and penile) cancers of a nonavalent HPV (9vHPV) vaccine program targeting MSM up to age 26 or age 45.

Methods: A dynamic transmission model was constructed stratified by age and HIV status to capture age-specific sexual behavior, and the impact of HIV status on disease progression. The cost-effectiveness of vaccinating MSM aged 18-26 or aged 18-45 years in Germany was assessed assuming additional vaccination uptake rates of 22.3%, 44.6%, and 60% for each of the two age groups. For each of the six resulting scenarios we estimated future cases of disease and death avoided, using 3% discount rate for costs from a payer perspective and quality-adjusted life years (QALYs) over 100 years. Additionally, incremental cost effectiveness ratios (ICERs) were compared to the basecase scenario (vaccination of 9-17 year-old boys only).

Results: Compared to the basecase scenario, vaccination of MSM aged 18-45 was projected to reduce anogenital cancers (independent of cause) among MSM by 30%-47% depending on the vaccination coverage rate achieved. If vaccination was limited to 18-26 year-old MSM, anogenital cancers and deaths decreased by 3851-7085 cases and 605-1127, respectively, depending on the vaccination coverage rate. If vaccination included 18-45 year-old MSM, anogenital cancers and deaths were projected to decrease by 5303-9296 and 832-1473, respectively, depending on the coverage rate. Vaccination up to the age of 45 had lower ICERs than vaccination up to the age of 26 when compared to basecase strategy. ICERs for vaccination of 18-45 year-old MSM in all three coverage scenarios ranged between 30,586-39,721 euros/QALY.

Conclusions: 9vHPV vaccination has a potential to considerably decrease anogenital cancer cases and related deaths of MSM in Germany. Vaccination up to age 45 was projected to be more cost-effective than vaccination up to age 26 and remained below the Gross Domestic Product (GDP) per capita threshold of 41,000 euros/QALY. These results are conservative as the comprehensive model additionally including oropharyngeal cancers and genital warts will further decrease the estimated cost per QALY gained and may help inform future vaccination policies.

#2223

34 - Economics and modelling

Costs of human papillomavirus vaccination in Tanzania: one-dose and two-dose estimates based on national program costs

Struckmann V[1], Stephani V[2], Mbando D[3], Changalucha J[4], Baisley K[5], Levin A[6], Hutubessy R[7], Watson-jones D[8], Quentin W[9]

[1]Technische Universität Berlin, Berlin, Germany

[2]Technische Universität Berlin, Berlin, Germany

[3]Mwanza Intervention Trials Unit, Mwanza, Tanzania

[4]Mwanza Intervention Trials Unit, Mwanza, Tanzania

[5]London School of Hygiene and Tropical Medicine, London, United Kingdom

[6]Levin & Morgan, Bethesda, United States

[7]World Health Organization, Geneva, Switzerland

[8]London School of Hygiene and Tropical Medicine, London, United Kingdom

[9]TECHNISCHE UNIVERSITÄT BERLIN, Berlin, Germany

Background/Objectives: Cervical cancer caused by human papillomavirus (HPV) is the most frequent cancer in women in many low-income countries, including Tanzania. Since 2014 the World Health Organization (WHO) recommends use of a routine two-dose schedule to protect against HPV infections. In 2018 the Tanzania government introduced a quadrivalent HPV vaccine into its immunization programme, targeting all 14 year-old girls with a two-dose vaccination schedule through school and health facility-based delivery. This study aimed to (1) estimate financial and economic costs of the Tanzanian vaccination programme; (2) assess the effect of alternative assumptions for future vaccination coverage rates and delivery strategies on estimated costs of vaccination, and (3) estimate the potential cost reductions resulting from a hypothetical one-dose vaccination schedule.

Methods: The WHO Cervical Cancer Prevention and Control Costing (C4P) tool was used to estimate the incremental financial and economic costs of the national vaccination programme from the perspective of the Tanzanian government. Data were collected from (a) national cost and coverage reports, (b) three costing workshop with stakeholders in Dar es Salaam, (c) interviews with regional, district, and health facility personnel in Mwanza region, and (d) observation of health workers in selected health facilities. Deterministic sensitivity analyses were performed to estimate the effect of alternative assumptions for coverage rates and delivery strategies as well as to assess the impact of a potential one-dose vaccination schedule.

Results:): Preliminary results indicate the total financial and economic costs for delivering 4.8 million doses of HPV vaccine in Tanzania between 2018 and 2022 wasUS$10.9 Million and US$37.2 Million respectively.Costs per dose were US$2.30 (financial) and US$7.78 (economic), and costs per fully immunised girl receiving two-doses of vaccine were US$5.27 (financial) and US$17.84 (economic). Cost estimates were relatively robust to different assumptions for delivery strategies and coverage rates. Costs per fully immunized girl would drop to US$2.56 (financial) and US$8.20 (economic) if one dose of HPV vaccine is found, through ongoing clinical trials, to be sufficient to protect girls from HPV infection.

Conclusions: This is one of the first studies to report national programme costs of an African HPV vaccination programme. Costs of a potential one-dose strategy would be significantly lower than the current two-dose strategies. These estimates of the costs of HPV vaccination are important for future cost-effectiveness analyses.

#2289

34 - Economics and modelling

EXPEDITING CERVICAL CANCER ELIMINATION IN THE NETHERLANDS WHILE BALANCING THE HARMS AND BENEFITS OF CERVICAL CANCER SCREENING

Jansen E[1], De Kok I[2], Kaljouw S[3], Demirel E[4], De Koning H[5], Hontelez J[6]

[1]ErasmusMC, University Medical Center Rotterdam, Rotterdam, Netherlands

[2]ErasmusMC, University Medical Center Rotterdam, Rotterdam, Netherlands

[3]ERASMUS MEDICAL CENTER , Delft, Netherlands

[4]ErasmusMC, University Medical Center Rotterdam, Rotterdam, Netherlands

[5]ErasmusMC, University Medical Center Rotterdam, Rotterdam, Netherlands

[6]ErasmusMC, University Medical Center Rotterdam, Rotterdam, Netherlands

Background/Objectives: Countries are striving to eliminate cervical cancer (CC) (i.e. incidence rate of <4.0 per 100.000 women) as fast as possible, by HPV vaccination and screening. However, intense screening also brings harms to individual women. Our aim was to find a balance between reaching CC elimination fast and maintaining an acceptable harms/benefits ratio of screening in the Netherlands.

Methods: The dynamic microsimulation model STDSIM and the MISCAN microsimulation model were integrated and applied to simulate HPV transmission and CC screening for the Dutch female population from 2022-2100. We evaluated the effects of 335 alternative vaccination and screening scenarios on both the year of CC elimination and the harms/benefits ratio of screening. In the status quo scenario, vaccination coverage would remain 55% with a bivalent vaccine and screening coverage remained 61% at 5 lifetime HPV screens. In alternative scenarios, all possible combinations were simulated where vaccination would be scaled up in steps of 10% up to 90%, the vaccine type was either bivalent or nonavalent, screening coverage was increased to 70% in steps of 5% and/or the number of lifetime HPV screens was decreased for vaccinated women or vaccinated cohorts to 0, 1, 2 or 3. The harms/benefits ratio was defined as the current number of women needed to be referred to a gynecologist to prevent one CC death (NNR), with the current NNR in unvaccinated women as the maximum acceptable harms/benefits ratio.

Results: Under status quo conditions, CC elimination will be reached in 2055. However, the NNR will increase with 41% compared to the current NNR in unvaccinated women. Under current vaccination conditions, elimination can be reached fastest in 2060 without increasing the NNR by inviting vaccinated cohorts for three lifetime HPV screens and increasing screening coverage to 70% (Figure 1). When vaccination would be scaled up to 90% coverage with the nonavalent vaccine, CC elimination will be reached in 2048 under status quo screening conditions. This will increase the NNR with 23%. However, if screening coverage could be increased to 70%, CC elimination could be reached in 2047 without increasing the NNR if vaccinated women are only invited for three lifetime HPV screens (Figure 1).

Conclusions: We show that expediting cervical cancer elimination in the Netherlands can best be achieved by scaling up HPV vaccination. This way, rapid elimination can be achieved while balancing the harms and benefits of screening. If vaccination will be scaled up, de-intensifying screening in vaccinated women will cause only little or no delay in the year CC elimination will be reached, but would prevent a lot of women being harmed by screening.

#2293

34 - Economics and modelling

OPTIMAL SCREENING STRATEGIES FOR UNVACCINATED WOMEN, WOMEN OFFERED QUADRIVALENT HPV VACCINATION AND WOMEN OFFERED NONAVALENT HPV VACCINATION IN THE U.S.: A CISNET COMPARATIVE MODELING ANALYSIS.

Naslazi E[1], Kate S[2], James K[3], Jane J. K[4], Cassie R[5], Jan A.c. H[6], Stephen S[7], Karen C[8], Inge M.c.m. D[9]

[1]Erasmus Medical Center, Rotterdam, Netherlands

[2]Cancer Research Division, Cancer Council NSW, Sydney, Australia

[3]Cancer Research Division, Cancer Council NSW, Sydney, Australia

[4]Harvard T.H. Chan School of Public Health, Boston, United States

[5]Harvard T.H. Chan School of Public Health, Boston, United States

[6]Erasmus Medical Center, Rotterdam, Netherlands

[7]Harvard T.H. Chan School of Public Health, Boston, United States

[8]Cancer Research Division, Cancer Council NSW, Sydney, Australia

[9]Erasmus Medical Center, Rotterdam, Netherlands

Background/Objectives: Women eligible for cervical cancer screening are currently a mix of cohorts who were not offered HPV vaccination (birth cohorts earlier than 1980), cohorts offered the quadrivalent vaccine (birth cohorts 1981-2002) and cohorts offered the nonavalent vaccine (born 2003 onwards). These cohorts will have markedly different risks of cervical cancer; however, screening recommendations do not currently take into account these differences. We performed a comparative modeling analysis through the Cancer Intervention and Surveillance Modeling Network (CISNET) aimed at evaluating optimal screening strategies for the three categories of birth cohorts.

Methods: We used three independent HPV microsimulation models to evaluate the optimal screening algorithms for three birth cohorts: females born in 1980 (unvaccinated), females born in 1993 (predominantly offered the quadrivalent vaccine) and females born in 2003 (offered the nonavalent vaccine). The models were calibrated to age-specific and type-specific HPV prevalence, HPV type distribution in precancer and cancer, and cervical cancer incidence and mortality in the US population and used standardized inputs regarding historical and future vaccination uptake, vaccine efficacy, cervical cancer screening algorithms, and costs. Costs and effects of 84 different screening strategies were evaluated for each cohort. Screening strategies varied by screening test (primary HPV testing with cytology or 16/18 genotyping triage and HPV and cytology co-testing), starting age (21, 25, 27 or 30 years) and interval (3, 5, 8 and 10-yearly).

Results: In all three models, for all three birth cohorts, strategies that incorporated primary HPV testing with 16/18 genotyping triage were more cost-effective than those with primary HPV testing with cytology triage and those involving co-testing. Screening every 3 or 5 years generally had higher cost-effectiveness ratios than screening every 8 or 10 years. All three models found that the optimal starting age of screening was 27 years for the 1980 and 1993 birth cohorts, and 30 years for the 2003 birth cohort, depending on the willingness to pay threshold.

Conclusions: Using three well-validated CISNET models, we assessed the cost-effectiveness of cervical cancer strategies in birth cohorts with differential cervical cancer risks. All models show that the optimal screening test was primary HPV with genotyping in all three birth cohorts. However, the younger birth cohorts have later optimal starting age of screening, depending on the WTP threshold. Primary HPV screening with genotyping holds promise as a generalizable strategy across unvaccinated and vaccinated cohorts and can be harnessed if optimization on HPV vaccination status is challenging.

FC10 - Anal HPV Infection

#2219

27 - Anal neoplasia

INCIDENCE AND RISK FACTORS OF ANAL SQUAMOUS CELL CARCINOMA IN COHORT STUDY OF PATIENTS WITH SEVERE ANAL INTRAEPITHELIAL NEOPLASIA AIN 3.

Valette E[1], Draullette M[2], Charpentier C[3], Roy C[4], Fantoli M[5], Radenne S[6], Pigot F[7], Juguet F[8], Petit P[9], Spindler L[10], Staumont G[11], Pernot S[12], Bord C[13], Godeberge P[14], Senejoux A[15], Garros A[16], Laurain A[17], Tarrerias A[18], Gault N[19], Abramowitz L[20]

[1]Hôpital Bichat, service de gastro-entérologie, Paris 75018, France

[2]Hôpital Bichat, service de gastro-entérologie, Paris 75018, France

[3]Hôpital Bichat, Laboratoire de Virologie, Paris 75018, France

[4]Hôpital Bichat, Paris 75018, France

[5]Cabinet médical, 25000 Besancon., France

[6]Hôpital de la croix rousse, Service de gastroentérologie, 69317 Lyon, France

[7]Hôpital Bagatelle, 33401 Talence., France

[8]Cabinet médical, 33000 Bordeaux, France

[9]Cabinet médical, 44000 Nantes, France

[10]Institut de coloproctologie Léopold Bellan, Groupe Hospitalier Paris Saint-Joseph, Paris 75014, France

[11]Clinique St Jean De Languedoc, 31400 Toulouse, France

[12]Hôpital HEGP, service de gastro-entérologie digestive, 75015 Paris, France

[13]Cabinet médical, 34000 Montpellier, France

[14]: Institut Mutualiste Montsouris, 75014 Paris, France

[15]Centre Hospitalier Privé, service de gastroentérologie, Saint Gregoire 35760, France

[16]Centre Hospitaliser Saint Joseph Saint Luc, 69007 Lyon, France

[17]Hôpital Bichat, service de gastro-entérologie, Paris 75018, France

[18]Hôpital Foch, 92150 Suresnes, France

[19]Hôpital Bichat,, Paris 75018, France

[20]Hôpital Bichat, service de gastro-entérologie, ,, France

Background/Objectives: The incidence of anal squamous cell carcinoma (SCC) is steadily increasing with 4153 new cases in 2013. It is preceded by severe anal intraepithelial neoplasia (AIN 3). However, the screening modalities of these lesions are not clearly established. The aim of our study was to determine the incidence and risk factors of anal SCC in patients with a history of AIN3.

Methods: We conducted a French multicenter ambispective cohort study from 2000 to 2020. Baseline demographic, clinical and behaviour data were collected at baseline and patients were followed up annually with anal smear and standard proctologic exam or high-resolution anoscopy (HRA).

Results: 978 patients were included in 28 French centers: 35.9 % from university hospital, 17.2 % from non university hospital and 46.9% from private activity. 56,3% of them were men, with a mean age of 49.5 years ± 12.9, most of the time caucasian type (92.5%). 390 patients (39.9%) were living with HIV at inclusion. 26.9% of women and 75.1% of men declared having anal intercourse. The first AIN3 lesion was diagnosed by standard proctologic exam in 52.7%, HRA in 6%, systematic examination of surgical specimen in 19.1% and by a combination of several diagnostic methods for 22.1%. After a median follow-up of 42.2 months (IC95% [39.6 - 44.9]), 54 patients (5.52%) developed anal SCC for a cumulative incidence at 36 months of 4.1 % ([2.9% - 5.8%]). At diagnosis, SCC were T1 in 60.4 %, T2 in 26.4 %, T3 in 11.3 % and T4 in 1.9 %. In univariate analysis, the factors significantly associated with the development of SCC were: older age at diagnosis (HR 1.05 [1.03-1.07]), type of inclusion center, and a history of genital HPV lesion in men (HR 2.36 [0.93-5.97]). Presence of P16/ki67 and high-risk HPV on the inclusion smear were also associated with higher risk of SCC in first analysis.

Conclusions: In this national multicenter AIN3 cohort, we found low incidence anal cancer and most of them were diagnosed at an early stage. Prognostic factors such as the mode and frequency of this follow-up will be analyzed.

#2225

27 - Anal neoplasia

IMPLICATIONS OF HPV STATUS ON CLINICAL OUTCOMES IN ANAL CANCER PATIENTS IN SCOTLAND

Guerendiain D[1], Grigorescu R[2], Graham C[3], Cuschieri K[4]

[1]Scottish HPV Reference Laboratory, NHS Lothian, Edinburgh, United Kingdom

[2]Pathology, NHS Lothian, Edinburgh, United Kingdom

[3]Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh, United Kingdom

[4]Scottish HPV Reference Laboratory, NHS Lothian, Edinburgh, United Kingdom

Background/Objectives: We assessed a population-based cohort of anal cancers collected in the east of Scotland during a 10-year period. HPV type specific status was determined and linked to disease outcomes. Our aims were to identify the component of vaccine preventable lesions, determine whether the fraction of HPV associated anal cancer is increasing and also understand whether HPV type or viral load are independently associated with patient outcomes.

Methods: A total of 224 anal biopsy samples from the Southeast of Scotland were collected between 2009 and 2018 as part of standard of care. HPV detection was performed using the Seegene Anyplex II HPV28 assay. Type specific prevalence was assessed in addition to the association(s) between HPV positivity and key demographic and clinical variables. Survival stratified by HPV status was assessed by Kaplan Meier and Cox models.

Results: A total of 208 samples had a valid result; 187 (89.90%, 95% CI 85.05 - 93.30) were HPV positive and 21 (10.1% 6.70 - 14.95) HPV negative. Types covered by the nonavalent vaccine were detected in 98.39% (95% CI 95.50 - 99.46) of the HPV positive cases. We found no evidence of a difference in HPV positivity according to year of diagnosis (p=0.256). In the univariate analysis, those over >70 y/o were more likely to be HPV negative (p<0.001) but no variable (age, stage, sex, recurrence) was associated with HPV positivity in the adjusted analysis. Preliminary data suggest that HPV positive cases had an improved survival; log-rank statistic (p=0.014); in the adjusted analysis, the hazard ratio (HR) was 0.28 (0.09 - 0.89) (p<0.001). Additionally, crude higher viral load was associated with improved survival in the adjusted analysis; log-rank (p=0.00059), however this was not shown to be significant in the adjusted analysis with a HR of 0.719 (0.19 - 2.66) (p=0.621).

Conclusions: The improved survival of HPV +ve (vs -ve) anal cancers is consistent with other HPV associated cancers including oropharynx and warrants further investigation. Crude analysis of HPV viral load was linked to improved clinical outcomes in the unadjusted analysis and work is underway to validate this observation using a ddPCR. The vast majority of HPV associated anal cancers in Scotland are vaccine preventable. Molecular interrogation of the HPV status anal cancer has significant for primary and secondary disease prevention strategies.

#2302

27 - Anal neoplasia

INDIVIDUAL PATIENT DATA META-ANALYSIS ON THE PROGNOSTIC SIGNIFICANCE OF P16INK4A AND HIGH-RISK HPV-TYPE DNA IN ANAL SQUAMOUS CELL CARCINOMAS

Obermueller T[1], Hautekiet J[2], Busto M[3], Reynders D[4], Belgioia L[5], Cats A[6], Gilbert D[7], Koerber S[8], Mai S[9], Meulendijks D[10], Rödel F[11], Yhim H[12], Hetjens S[13], Weiß C[14], Rasmussen C[15], Urbute A[16], Verdoot F[17], Kjaer S[18], Reuschenbach M[19], Goetghebeur E[20], Von Knebel Doeberitz M[21], Arbyn M[22], Prigge E[23]

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

[2]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium

[3]Unit of Cancer Epidemiology, Belgian Cancer Centre and Scientific Sciensano, Brussels, Belgium

[4]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium

[5]Health Science Department (DISSAL), University of Genoa and Department of Radiation Oncology, IRCCS San Martino Hospital, Genoa, Italy

[6]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

[7]Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, United Kingdom

[8]Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany

[9]Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

[10]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

[11]Department of Radiotherapy and Oncology, Goethe-University, Frankfurt A.m., Germany

[12]Division of Hematology/Oncology, Jeonbuk National University Medical School, Jeonju, South Korea

[13]Department of Biometry and Statistics, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

[14]Department of Biometry and Statistics, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

[15]DANISH CANCER SOCIETY RESEARCH CENTRE, , Denmark

[16]Unit of Virus, Lifestyle, and Genes, Danish Cancer Society Research Centre, Copenhagen, Denmark

[17]Unit of Virus, Lifestyle, and Genes, Danish Cancer Society Research Centre, Copenhagen, Denmark

[18]Unit of Virus, Lifestyle, and Genes, Danish Cancer Society Research Centre , Copenhagen, Denmark

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

[20]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium

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

[22]Unit of Cancer Epidemiology, Belgian Cancer Centre and Scientific Sciensano, Brussels, Belgium

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

Background/Objectives: High-risk human papillomaviruses (hrHPV) play an etiological role in the pathogenesis of the majority of anal squamous cell carcinomas (ASCC) as indicated by the simultaneous detection of the surrogate markers hrHPV DNA and p16INK4A (p16) in tumor tissue. It has been suggested that these two markers also have prognostic relevance in ASCC patients by analogy to other HPV-driven cancer entities, such as oropharyngeal cancers. However, previous studies have reported heterogenous data on the prognostic significance of hrHPV DNA and p16 status in ASCC patients. Our individual patient data (IPD) meta-analysis aims to determine the prognostic relevance of oncogenic HPV DNA and p16 alone or in combination in ASCC patients while controlling for confounding variables.

Methods: All published studies analyzing overall survival (OS) and p16 expression by immunohistochemistry alone or in combination with hrHPV DNA in ASCC patients were identified by a broad search string. Authors of potentially eligible studies were contacted to obtain individual patient data. OS was analyzed by Cox-Regression using p16 and hrHPV DNA, and adjusted for relevant covariates.

Results: Out of nineteen potentially eligible studies, IPD obtained from seven studies could be included in the final meta-analysis. Among five studies providing data on both hrHPV DNA and p16, 76% of 459 ASCC were p16+/hrHPV DNA+. Eleven percent of ASCC were negative for both markers, while discordant results for hrHPV DNA and p16 were observed in 13% of cases. The pooled three-year OS rate was superior in patients with p16+/hrHPV DNA+ ASCC (86% (95% CI 82-90%)) compared to patients with p16-/hrHPV DNA- ASCC (39% (95% CI, 24-54%)). In patients with a discordant p16 and hrHPV DNA status, three-year OS rates of 75% (95% CI, 56-86%) (p16+/hrHPV DNA-) and 55% (95% CI, 35-71%) (p16-/hrHPV DNA+) were observed.

Conclusions: This IPD meta-analysis demonstrates that both hrHPV DNA and p16 overexpression are present in 76% of ASCC, indicating etiological relevance of HPV in this proportion of cases. The combined detection of hrHPV DNA and p16 in ASCC predicts a favorable OS for the affected patients, supporting considerations on potential treatment de-escalation strategies in this distinct patient group to reduce therapy-associated morbidity.

#2313

27 - Anal neoplasia

A SYSTEMATIC REVIEW AND META-ANALYSIS OF CYTOLOGY AND BIOMARKERS FOR ANAL CANCER SCREENING

Clarke M[1], Wentzensen N[2]

[1]National Cancer Institute, NIH, Rockville, United States

[2], , United States

Background/Objectives: Like cervical cancer, most anal squamous cell cancers are caused by high-risk HPV infection. Given the common etiology between anal and cervical carcinogenesis, anal cancer screening has been proposed for some high-risk groups using strategies adapted from cervical cancer prevention. The International Anal Neoplasia Society assembled a Task Force to develop recommendations for anal cancer screening. A critical component of this process is to evaluate diagnostic tests for anal precancer and cancer to make recommendations for clinical use. We conducted a systematic review and meta-analysis to evaluate tests for anal cancer screening.

Methods: We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including studies evaluating the performance of tests and biomarkers for anal cancer screening. We searched English-language, peer-reviewed studies published or under peer review before 07/2020. We screened titles and abstracts for inclusion and reviewed full-text articles to determine eligibility. We calculated pooled sensitivity and specificity by fitting a bivariate random effects model. We used data abstracted on cases of anal precancer (anal HSIL+ or AIN2+, "AIN2+") and non-cases (<HSIL or <AIN2) to estimate pooled absolute risks using multilevel logistic-normal random effects models.

Results: Of the 3,045 articles identified, 40 were included. Among all studies, the pooled prevalence of AIN2+ was 22% (95% CI, 17-28%) and ranged from 1% to 68% across studies. Several of these studies were of poor or moderate quality. In the 35 studies assessing cytology, the sensitivity and specificity were 78.6% and 51.6%, respectively. In the 26 studies evaluating HPV testing, the sensitivity was 93.5% and specificity was 34.6%, with a lower risk in those testing negative (5% vs. 11%), but higher test positivity (76% vs. 58%), compared to cytology. HPV E6/E7 mRNA and p16/Ki-67 dual stain had variable performance in few studies (n=5, respectively), and were less sensitive (73.7% and 67.5%, respectively), but more specific (63.6% and 69.2%), compared to cytology.

Conclusions: Among all studies, there was heterogeneity in the baseline risk of anal precancer, and several studies were of low quality.HPV testing was highly sensitive, but the high positivity makes it less useful as an anal screening test, since few screened individuals are negative. Anal cytology was the most well-studied screening approach and provided better risk stratification than HPV testing. More data on other HPV-associated biomarkers are needed from well-designed studies.

FC13 - HPV Testing / Molecular Markers II

#2279

8 - HPV testing

DEVELOPTMENT OF HPV TESTING IN MEN IN A ROUTINE DIAGNOSTIC LABORATORY

Stary A[1], Schwarz K[2], Mühlberger J[3]

[1]Pilzambulatorium, Wien, Austria
[2]Pilzambulatorium, Vienna, Austria
[3]Pilzambulatorium, Vienna, Austria

Background/Objectives: Recent studies have shown that infections with HPV are no longer a burden that solely affects women. Even though men are less prone to HPV associated malignancies, they play an important role in transmission of HPV to women. To monitor HPV infections in both genders, routine HPV testing in men is finding its way into the diagnostic world. The aim of this study was to analyse the needs and requirements for successful HPV testing in men in a routine diagnostic laboratory.

Methods: To perform good routine testing, aspects such as sample collection, appropriate swabs and type of collection need to be adapted accordingly. For this study we included 832 male samples to evaluate the most frequent sampling sites. To compare two different collection devices based on performance and failure rate, the first 200 samples were collected in duplicate using CerviBrush and FLOQSwabs®. Subsequently, further 632 samples were only collected with FLOQSwabs®. Penile, perigenital, pharyngeal and anorectal specimens were tested for HPV at the Outpatient´s Centre for Diagnosis of Infectious Venero-dermatological diseases by using the PapilloCheck®. It is a microarray-based assay which allows the simultaneous detection and identification of 18 high risk (hr) and 6 low risk (lr) HPV genotypes. Analysis of the results was performed using the CheckScannerTM software.

Results: HPV prevalence in men was around 50%. The most frequent sampling sites include the urethral orifice and glans penis (59%), mons pubis (7.8%), and anal region (7.5%). Regarding the collection device, it has been shown that the FLOQSwabs® has an approximately 50% lower rate of invalid results and detects more HPV genotypes in men compared to the CerviBrush. The main reason for failure was an insufficient amount of cellular material. Among the anal samples, the PCR control gives a weak signal in 21%, which suggests an inhibited PCR performance.

Conclusions: The high prevalence of HPV infections in men shows that routine testing is justified. To generate a high-quality sample, it is important to have a device that can collect as much cellular material as possible from a dry or scaly surface. In this study, FLOQSwabs® proved to be a better device for male sample collection.

#2287

8 - HPV testing

ALTERNATIVE CHEMISTRIES FOR TEST OF CURE (TOC) - A RETROSPECTIVE CASE-CONTROL STUDY

Elasifer H[1], Bhatia R[2], Graham C[3], Asodaria P[4], Cuschieri K[5]

[1]HPV Research Group, Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom, Edinburgh, United Kingdom

[2]Scottish HPV Reference Laboratory, NHS Lothian, Edinburgh, United Kingdom, Edinburgh, United Kingdom

[3]Edinburgh Clinical Research Facility, University of Edinburgh, Edinburgh, United Kingdom, Edinburgh, United Kingdom

[4]HPV Research Group, Centre for Reproductive Health, University of Edinburgh, Edinburgh, United Kingdom, Edinburgh, United Kingdom

[5]Scottish HPV Reference Laboratory, NHS Lothian, Edinburgh, United Kingdom, Edinburgh, United Kingdom

Background/Objectives: The high sensitivity of HPV testing renders it a credible method for monitoring the success of treatment for women treated for high-grade lesions as a "test of cure" (TOC). In Scotland, TOC is carried out by performing a combined HPV and cytology test, six months post-treatment. While there is much data on the performance of the clinically validated HPV assays in screening and triage contexts, there is a paucity of data on their discrete performance in the post-treatment setting.

Methods: Since 2012, over 40,000 women have been through the TOC pathway in Scotland, with the majority tested by the Abbott RealTime HPV test. We performed a retrospective case-control study of 446 residual stored samples where an RNA based test (The Aptima HPV test, Hologic) was applied to 223 samples and a DNA based test (The Alinity HPV test, Abbott) was applied the other 223 samples. Each sample panel included 63 cases (women who had "failed" TOC and went on to have residual or recurrent ≥CIN2 post-treatment) and 160 controls (women who passed TOC and had negative or ≤CIN1 histology at 3-year follow-up OR women who failed TOC but had ≤CIN1 on followup). The clinical performance of the assay(s) was performed at the level of CIN2+ and CIN3+ and compared to the original result generated as part of the "routine" TOC programme (RealTime HPV Test, Abbott).

Results: The results are encouraging in that both the DNA and RNA based assays have a high sensitivity for the detection of ≥CIN2 and ≥CIN3 in the TOC population. Given the additional risk of disease in women treated for high-grade lesions, sensitivity is a key parameter. Sample Panel Assay Sensitivity, CIN2+ Specificity, <CIN2 Sensitivity, CIN3+ Specificity, <CIN3 A Aptima 96.83% (95% CI: 88.01- 99.45) 85.81% (95% CI: 79.08- 90.70) 100% (95% CI: 87.69- 100) 73.77% (95% CI: 66.67- 79.85) RealTime 93.65% (95% CI: 83.75 - 97.95) 81.25% (95% CI: 74.15- 86.81) 97.14% (95% CI: 83.38 - 99.85) 70.74% (95% CI: 63.60- 77.02) B Alinity 93.44% (95% CI: 83.25- 97.88) 82.46% (95% CI: 75.33- 87.93) 94.12% (95% CI: 78.94- 98.97) 71.27% (95% CI: 64.00- 77.62) RealTime 98.41% (95% CI: 90.32-99.92) 82.46% (95% CI: 75.33- 87.93) 97.14% (95% CI: 83.38-99.85) 72.34% (95% CI: 65.27-78.48)

Conclusions: The Aptima and RealTime assays, as well as The Alinity and RealTime assays, shows excellent concordance. Although evaluation of the assays was performed on samples stored for up to 6- years, both showed comparable results to the original assay result.

#2180

18 - Microbiome

COLLECTION AND STABILIZATION OF URINE SAMPLES WITH THE COLLI-PEE® DEVICE AND REAGENT TO FACILITATE URINARY MICROBIOME STUDIES

Macdonald K[1], Wood C[2], Macklaim J[3], Arora A[4], Doukhanine E[5], Faster D[6], Vankerckhoven V[7], Beyers K[8], Iwasiow R[9]

[1]DNA GENOTEK, Ottawa, Canada
[2]DNA Genotek, Ottawa, Canada
[3]DNA Genotek, Ottawa, Canada
[4]DNA Genotek, Ottawa, Canada
[5]DNA Genotek, Ottawa, Canada
[6]NOVOSANIS, Wijnegem, Belgium
[7]Novosanis NV, Wijnegem, Belgium
[8]Novosanis NV, Wijnegem, Belgium
[9]DNA Genotek, Ottawa, Canada

Background/Objectives: It is now recognized that urine is not sterile under healthy conditions, and harbors bacteria and other microorganisms. In response to disorders, including genitourinary malignances1, sexually transmitted infections (STIs)2, and urolithiasis3, the urinary microbiome can alter its taxonomic makeup and microbial distribution. Due to its low microbial biomass, urine requires controlled sample collection and efficient DNA extraction methods for microbiome studies. Additionally, collected urine samples, if not processed immediately, are at risk for microbial proliferation and/or lysis, resulting in a microbiome profile no longer representative of in vivo, making longitudinal or home-based sample collection challenging. A simple, standardized collection method combined with an effective urine stabilization chemistry would therefore be extremely beneficial for urinary microbiome studies.

Methods: Midstream urine was collected from healthy female and male donors using Novosanis" Colli-Pee®, an at-home self-sampling device designed for standardized and volumetric urine collection, which contained a proprietary urine stabilization reagent. Samples were processed immediately (baseline), or held at ambient temperature for 14 days with or without freeze/thaw cycling (to mimic transport conditions) until processed. Urine samples were centrifuged, with the cellular pellet used for DNA extraction using standard microbiome methodologies. Total DNA content was determined by Picoquant, with bacterial DNA content assessed via 16S qPCR. Species level microbiome profiles of the samples were determined by shotgun metagenomic sequencing.

Results: Using Colli-Pee®, all female midstream urine samples, and a subset of male samples, yielded sufficient microbial DNA quantities for shotgun metagenomic sequencing prior to and following storage. The urine stabilization chemistry effectively preserved the total DNA and bacterial DNA content of the samples over time. Female and male microbiome profiles clustered seperately, as expected. Importantly, the species level microbiome profiles of the urine samples were stabilized from baseline to storage endpoint (as measured by Bray Curtis distance).

Conclusions: Colli-Pee® combined with proprietary urine microbial stabilization reagent offers an exciting and effective opportunity to study the urinary microbiome impact on health and disease by facilitating home-based and longitudinal sample collection. This ability to stabilize the urinary microbiome will assist research into its association with HPV infection/disease progression in females and males, especially given Colli-Pee®"s success in collecting HPV analytes in urine.

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#2404

8 - HPV testing

Evaluation of the fully automated NeuMoDx HPV Assay for cervical cancer screening

Hesselink B[1], Meijer C[2], Heideman D[3], Doorn S[4], Craig E[5], Wu B[6], Brahmasandra S[7]

[1]SELF-SCREEN B.V., Amsterdam, Netherlands

[2]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Leiden, Netherlands

[3]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[4]Self-screen B.V., Amsterdam, Netherlands

[5]QIAGEN, Ann Arbor, United States

[6]QIAGEN, Ann Arbor, United States

[7]QIAGEN, Ann Arbor, United States

Background/Objectives: High-risk human papillomavirus (HPV) testing provides better protection against cervical cancer compared to cytology. As a consequence, cervical screening by primary HPV testing has or will be implemented in multiple countries or regions thereof. This emphasizes the need for robust high-throughput HPV testing solutions. The NeuMoDx HPV Test Strip is a clinically validated CE-IVD in vitro real-time PCR-based assay for the qualitative detection of HPV DNA, targeting the E7 region of 15 HPV genotypes (i.e.,16,18,31,33,35,39,45,51,52,56,58,59,66,67 and 68) and provides separate genotype information for HPV16 and HPV18. Implemented on the fully automated NeuMoDx Molecular System, it offers a high-throughput "sample to result" HPV test named NeuMoDx HPV Assay. This study reports on the analytical and clinical performance of the NeuMoDx HPV Assay.

Methods: The following analytical performance metrics of the NeuMoDx HPV Assay were studied: stability, limit of detection (LoD) of each genotype, specificity against non-target organisms and impact of interfering substances. Clinical performance for CIN2+ was evaluated according to international guidelines for HPV DNA test requirements for cervical cancer screening purpose.

Results: All the reagents and consumables are stable at ambient conditions, do not require refrigeration and have ready-to-use configurations requiring no user mediated steps. The LoD of the NeuMoDx HPV Assay was determined to be competitive with the QIAscreen HPV PCR Test. No cross-reactivity was observed against non-target microorganisms. No interference was demonstrated in the presence of endogenous and exogenous interfering moieties as well as commensal organisms. Turnaround time for the complete test was ~60 minutes, with no user monitoring required once the samples and reagents were loaded. Clinical performance metrics fulfilled the guidelines.

Conclusions: The NeuMoDx HPV Test Strip as implemented on the NeuMoDx Molecular System is a rapid, easy to use, clinically validated test for detection of high-risk HPV with HPV16 and HPV18 genotype information from cervical screening samples.

#2398

14 - Screening methods

PERFORMANCE OF HPV E6/E7 mRNA ASSAY AS PRIMARY SCREENING TEST. RESULTS FROM THE NTCC2 TRIAL

Giorgi Rossi P[1], Carozzi F[2], Ronco G[3], Allia E[4], Bisanzi S[5], Gillio-tos A[6], Demarco L[7], Rizzolo R[8], Gustinucci D[9], Del Mistro [10], Frayl H[11], Massimo C[12], Iossa A[13], Cesarini E[14], Bulletti S[15], Passamonti B[16], Gori S[17], Toniolo L[18], Barca A[19], Bonvicini L[20], Mancuso P[21], Ventuurelli F[22], Beenevolo M[23]

[1]AUSL-IRCCS DI REGGIO EMILIA, Reggio Emilia, Italy

[2]ISPRO Toscana, Florence, Italy

[3]INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, Torino, Italy

[4]CPO Piemonte, Torino, Italy

[5]REGIONAL CANCER PREVENTION LABORATORY OF ISPRO, Florence, Italy

[6]CPO Piemonte, Torino, Italy

[7]CPO Piemonte, Torino, Italy

[8]CENTRE FOR CANCER PREVENTION, Turin, Italy

[9]USL 1 Umbria, Perugia, Italy

[10]ISTITUTO ONCOLOGICO VENETO, Padova, Italy

[11]Istituto Oncologico Veneto, Padova, Italy

[12]ISPRO Toscana, Florence, Italy

[13]ISPRO Toscana, Florence, Italy

[14]USL 1 Umbria, Perugia, Italy

[15]USL 1 Umbria, Perugia, Italy

[16]USL 1 Umbria, Perugia, Italy

[17]VENETO INSTITUTE OF ONCOLOGY IOV-IRCCS, Padova, Italy

[18]AULSS 6 Veneto, Este, Italy

[19]Regione Lazio, Roma, Italy

[20]AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

[21]AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

[22]AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

[23]IRCCS - Regina Elena National Cancer Institute, Roma, Italy

Background/Objectives: The NTCC2 study (1) allows to estimate the performance of E6/E7 mRNA overexpression as primary screening test with different alternative strategies to triage HPV-positive women.

Methods: All HPV DNA-positive women and a sample of HPV DNA-negative women were tested for E6/E7 mRNA using the APTIMA assay (Hologic). HPV DNA-positive women were all tested for cytology and p16/ki67. Women with positive cytology were referred to colposcopy, while those negative were randomised to immediate colposcopy or to 1-year HPV DNA retesting. We have assumed that no CIN2+ or CIN3+ would be missed by the 1-year HPV DNA retesting. Data allowed estimating a relative sensitivity (compared to HPV-DNA), referral rate and positive predictive value (PPV) of E6/E7 mRNA followed by colposcopy for all positive women, with cytology or p16/ki67 dual staining triage. All CIN2+ lesions found within 24 months of follow up were included.

Results: Among the 41127 women recruited, 3180 (7.7%) were HPV DNA positive and, among them 2112 were mRNA positive. Overall, 176 CIN2+ (97 CIN3+) were found. A sample of 1108 HPV DNA-negative women were tested for mRNA and 10 (0.9%) were positive, even though no cytologic or histologic abnormalities were found in this group. The estimated specificity was 94.5% (95% CI 94.2% - 94.7%). The total estimated positivity rate was 6.0%. and the relative sensitivity to HPV DNA for CIN2+ was 94.2% (95% CI 90.5% - 97.1%) and for CIN2+ and CIN3+ was 96.8% (95% CI 91.4% - 99.1%).If all mRNA-positive women were referred to colposcopy, PPV would have been 8.2%. Adopting cytology triage for mRNA positive women would reduce immediate referral to 1.7% and PPV would increase to 18.5%, while total colposcopy referral, including the cases with HPV DNA-positivity at 1-year retesting, would be 4.9%, obtaining an overall PPV of 8.7%. Adopting p16/ki67 as triage for mRNA-positive women immediate referral would be 2.0%, with an immediate PPV of 20.3%, while the total colposcopy referral would be 4.9%, obtaining an overall PPV of 8.7%.

Conclusions: The HPV E6/E7 mRNA assay used as primary screening test, would miss about 5% of the CIN2+ and even less CIN3+. Overall positivity would be about 25% lower than that of HPV DNA. Triage with cytology or p16/ki67 dual staining would not substantially improve the overall performance of the screening algorithm if retesting of mRNA-positive/triage-negative women is performed with HPV DNA after 12 months.

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#2286

11 - Genotyping

EXTENDED GENOTYPING IN A HPV POSITIVE PRIMARY SCREENING POPULATION, USING THE BD ONCLARITY HPV ASSAY

Naik P[1], Keegan H[2], White C[3], Reynolds S[4], O' Brien R[5], Pilkington L[6], O' Toole S[7], Tewari P[8], O' Leary J[9], Marin C[10]

[1]TRINITY COLLEGE DUBLIN AND COOMBE WOMEN & INFANTS UNIVERSITY HOSPITAL, , Ireland

[2]Coombe Women & Infants University Hospital, Dublin, Ireland

[3]Coombe Women & Infants University Hospital, Dublin, Ireland

[4]Coombe Women & Infants University Hospital, Dublin, Ireland

[5]Coombe Women & Infants University Hospital, Dublin, Ireland

[6]Coombe Women & Infants University Hospital, Dublin, Ireland

[7]Trinity College Dublin, Dublin, Ireland

[8]Trinity College Dublin, Dublin, Ireland

[9]Trinity College Dublin and Coombe Women & Infants University Hospital, Dublin, Ireland

[10]Trinity College Dublin, Dublin, Ireland

Background/Objectives: In April 2020, Ireland switched to HPV primary based cervical screening with reflex to cytology as triage. Prior to the roll-out of HPV primary screening, in 2015, the Irish Cervical Screening Consortium (CERVIVA), in partnership with CervicalCheck, undertook an HPV Primary Screening Pilot Study of >13,000 women to investigate different approaches for triage of HPV positive women. The BD Onclarity HPV test is being evaluated as a triage option on HPV positive specimens from this larger observational prospective study.

Methods: The BD Onclarity HPV test, targets HPV E6/E7 DNA and offers extended genotyping of 14 high-risk HPVs as either individual (16, 18, 31, 45, 51 and 52) or as grouped genotypes (P1: 33/58, P2: 56/59/66, P3: 35/39/68). In this study, to date, the performance of the BD Onclarity HPV test (on BD Viper LT) has been evaluated on an aliquot of frozen PreservCyt from 955 HPV positive and 71 HPV negative specimens from participants enrolled in the CERVIVA HPV Primary Screening Study.

Results: Baseline HPV prevalence using Cobas 4800 HPV test in this population was 16%. Overall agreement between the Cobas 4800 HPV test and the BD Onclarity HPV test for the detection of HPV was 86% (95% CI 0.85-0.86, k= 0.4). The distribution of HPV genotypes detected using BD Onclarity HPV test was: HPV16 (22%), P2 group (56/59/66); (22%), P3 group (35/39/68); (15%), HPV31 (12%), P1 group (33/58); (10%), HPV52 (10%), HPV51 (8%), HPV18 (7%) HPV45 (7%). There was 95% agreement between Cobas 4800 HPV test and BD Onclarity HPV test for detection of HPV16 (95% CI 0.95-0.96, k= 0.875) and 98% for detection of HPV18 (95%CI 0.983-0.985, k= 0.885). The overall cytology breakdown was as follows: 5% (HSIL, ASCUS-H, AGUS/AIS), 22% (ASCUS and LSIL), 71% (NILM) and 1% inadequate. Overall, agreement of the 2 assays across the cytological categories was: 98% (HSIL/ASC-H/AGC/AIS), 95% (ASCUS/LSIL) and 82% (NILM). There were 142 (15%) discordant results between the 2 tests, of which 90% had NILM cytology. The Cobas 4800 HPV test Ct value for discordant specimens ranged from 27.1 to 40.5, with an average of 37.3 and 81% had Ct value >35.

Conclusions: There is good agreement overall between the Cobas 4800 HPV test and BD Onclarity HPV test, in particular for HPV16 and HPV18. Where discrepancies occurred, they were associated with NILM cytology or potentially low viral copy as indicated by late Ct values. Extended genotyping may offer additional potential for triage of HPV positive women from primary screening.

FC11 - HPV Vaccines II

#1948

35 - Advocacy, acceptability and psychology

Advocating for HPV disease elimination in Europe

Baker P[1], Kelly D[2], Medieros R[3]

[1]European Cancer Organisation, Brussels, Belgium
[2]European Cancer Organisation, Brussels, Belgium
[3]European Cancer Organisation, Brussels, Belgium

Background/Objectives: The elimination of cancers and other diseases caused by HPV as a public health problem is now a realistic possibility. The European Cancer Organisation has responded to this challenge by launching a new advocacy campaign for HPV elimination across the 53 member states of the WHO European region. The impact of COVID-19 on HPV vaccination and cervical cancer screening programmes, all-cancer diagnosis and treatment, and also public attitudes to vaccination generally, adds a new urgency to this work. With the WHO launching a global strategy on the elimination of cervical cancer in August 2020 and a new EU Beating Cancer Plan scheduled for early 2021, this is an opportune time for advocacy in this field.

Methods: The European Cancer Organisation's HPV Action Network was launched at a meeting at the EU Parliament in December 2019. It aims to achieve gender-neutral vaccination and equitable access to effective screening programmes and treatments. It also makes the case for action to improve practitioners' knowledge of HPV issues and to increase public awareness. The campaign is following the example of the effective advocacy on gender-neutral vaccination led by HPV Action in the UK by developing a broad-based, multi-disciplinary network of organisations and individuals. The European Cancer Organisation, with 28 European cancer member societies and 17 European patient advocacy groups, already has close links with EU Health Commissioner Stella Kyriakides. A major policy statement, Viral Protection: Achieving the Possible - A Four Step Plan for Eliminating HPV Cancers in Europe, was published in September 2020 and forms the core of the case for action. The 2020 European Cancer Summit, held in November, provided an opportunity to review progress and maintain momentum with key policymakers and politicians, as well as oncology specialists and patient advocates. The presentation will outline the rationale for action and the current and future work of the campaign, including the means by which scientists, practitioners and others can give powerful forms of support to the achievement of its goals. The plans include researching the implementation of gender-neutral vaccination and cervical cancer screening across Europe, identifying gaps in policy and practice, and advocacy at the regional and national levels. It is envisaged that national advocacy work will be led by 'national HPV ambassadors' supported by networks of organisations and individuals.

Results: The impact of the work to date will be presented, including the coverage of HPV issues in Europe's Beating Cancer Plan.

Conclusions: Progress on the scientific and clinical aspects of HPV, not least their implementation, will be accelerated by the right policy environment. The European Cancer Organisation is leading the campaign for policy change in this field and believes that, by 2030, it is entirely feasible for every European country to have in place gender-neutral HPV vaccination and high-precision cervical cancer screening programmes both with high levels of uptake. The support of all those who share these critically important objectives is very welcome.

#2276

5 - HPV prophylactic vaccines

Effectiveness of HPV vaccination against cervical neoplasia among birth cohorts ineligible for routine vaccination: A population-based study

Li D[1], Mari N[2], Nathalie S[3], Ole K[4], Bo H[5]

[1]DEPARTMENT OF RESEARCH, CANCER REGISTRY OF NORWAY., Oslo, Norway

[2]Department of Research, Cancer Regist, Oslo, China

[3]Department of Research, Cancer Registry of Norway, Oslo, China

[4]Department of Research, Cancer Registry of Norway, Oslo, China

[5]Department of Research, Cancer Registry of Norway, Oslo, China

Background/Objectives: Background The HPV vaccine is prophylactic and has lower efficacy among women who have previous exposure to HPV. HPV exposure is strongly age-dependent, and women who get the HPV vaccine outside the routine program tend to be considerably older than those eligible for routine HPV vaccination. We aimed to assess the risk of cervical neoplasia grade 2 or worse (CIN2+) and grade 3 or worse (CIN3+) associated with HPV vaccination status stratified by age at vaccine initiation, in birth cohorts outside the routine HPV vaccination program in Norway.

Methods: Methods We performed an observational study of all women born in 1975-1996 and resident in Norway during 2006-2016 by linking nation-wide individual-level registry data on sociodemographic information, HPV vaccination status and cervical neoplasia. Incidence rate ratios (IRRs) and 95% confidence intervals (CI) for CIN2+ and CIN3+ by HPV vaccination status were estimated with Poisson regression models adjusted for attained age, household income and screening year. Separate models were performed for women vaccinated before age 20, and at age 20 or older.

Results: Results 47683 individuals initiated HPV vaccination outside the routine program by the end of 2016, of which only 8904 initiated before age 20. The incidence of CIN2+ and CIN3+ increased with attained age regardless of vaccination status and age at vaccination initiation (all $p < 0.01$). Compared to unvaccinated women, the incidence rate of CIN2+ was lower among women who initiated HPV vaccination before age 20 (IRR 0.69, 95% CI 0.50-0.95), while it was higher among women who initiated HPV vaccination at age 20 or older (IRR 1.20, 95% CI 1.00-1.44). Similar results were found for CIN3+.

Conclusions: Conclusions Age at vaccination is clearly important for HPV vaccine effectiveness at the population level. HPV vaccination was effective against CIN2+ and CIN3+ in girls and women who initiated HPV vaccination outside the routine program before age 20. HPV vaccination at older ages appears inefficient in protecting against cervical neoplasia at the population level in Norway. Further investigation is warranted to address whether self-selection for HPV vaccination outside the routine program may be associated with risk for previous HPV infection.

#2218

5 - HPV prophylactic vaccines

Incidence of new-onset autoimmune conditions among males receiving GARDASIL®

Marks M[1], Amend K[2], Turnbull B[3], Zhou L[4], Velicer C[5], Saddier P[6], Seeger J[7]

[1]MERCK, West Point, United States

[2]OPTUM, Boston, United States

[3]Optum, Boston, United States

[4]Optum, Boston, United States

[5]MERCK & CO., Kenilworth, Nj, United Kingdom

[6]MERCK & CO., INC., West Point, United States

[7]Optum, Boston, United States

Background/Objectives: The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine) was approved for use in males in the United States (US) in 2009. This study's objective was to describe the incidence of new-onset of autoimmune disorders (AIDs) among males receiving the 4vHPV vaccine.

Methods: A US healthcare claims database was used to identify males receiving 4vHPV vaccine as well as potential AIDs. Males of any age who received at least one dose of 4vHPV vaccine with continuous healthcare database membership for at least 12 months prior to their first dose (i.e., baseline period) were identified. Males not receiving 4vHPV vaccine having a physician's office visit at the same time as a vaccinated male were identified as comparators and propensity-score matched to the vaccinated males. Twenty AIDs comprising four conditions groups (Rheumatology/Hematology, Gastroenterology, Endocrinology and Neurology) were identified using ICD-9/ICD-10 diagnosis codes. Individuals with a code for a given AID in the baseline period were excluded from analyses of that AID. Medical chart review and adjudication were conducted to confirm case status and define the timing of clinical onset. Confirmed cases with clinical onset within a risk period of 6-months following a vaccine dose (or up to 18 months following an office visit for comparators) were included for incidence analysis. Incidence rates (events per 1,000 person-years) were calculated for the matched vaccinated and comparator groups, and compared using relative rate (RR) ratios.

Results: Between 2009 and 2016, a total of 65,606 males (mean age: 15 years) receiving at least one dose of 4vHPV vaccine were identified, including 55,670 matched to an equal number of comparators, contributing 39,735 and 58,215 person-years, respectively. A total of 416 and 373 potential AIDs were identified based on diagnostic codes among the vaccinated and comparators. Following adjudication, 35 and 47 AIDs were confirmed as new-onset within the risk period for vaccinated males and comparators, respectively. The incidence of any AID was similar among vaccinated (0.88 [95% CI: 0.61-1.23]) and comparators (0.81 [0.59-1.07]). The RR was 1.09 [0.70-1.69] overall; 0.49 [0.1-2.42] for rheumatology/hematology, 1.26 [0.58-2.71] for gastroenterology, 1.11 [0.61-2.02] for endocrinology and 1.46 [0.21-10.4] for neurology condition groups.

Conclusions: The incidence rate of new-onset AIDs among males enrolled in a US healthcare claims database was similar among vaccinated individuals and unvaccinated comparators. These results are consistent with other studies and the known safety profile of the 4vHPV vaccine.

#2222

5 - HPV prophylactic vaccines

Vaccine effectiveness following routine immunization with bivalent HPV vaccine: Protection against genital HPV infections following two doses is comparable to three doses

Hoes J[1], King A[2], Schurink-van 't Klooster T[3], Berkhof J[4], Bogaards J[5], De Melker H[6]

[1]RIVM - DUTCH NATIONAL INSTITUTE FOR PUBLIC HEALTH AND THE ENVIRONMENT, Hoofddorp, Netherlands

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

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

[4]VRIJE UNIVERSITEIT AMSTERDAM, Amsterdam, Netherlands

[5]Department of Epidemiology & Data Science, Amsterdam UMC, Amsterdam, Netherlands

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

Background/Objectives: In the Netherlands, the bivalent HPV vaccine (2vHPV) has been offered to preadolescent girls via the National Immunization Program (NIP) in a three-dose (3D) schedule from 2010 onwards, but was replaced by a two-dose (2D) schedule in 2014. The current study estimates vaccine effectiveness (VE) against HPV infections among girls eligible for routine 2D immunization. This is one of the first observational studies investigating the effectiveness of reduced-dosing schedules in a regular immunization program setting. We report data up to four years post-vaccination.

Methods: Data were used from a longitudinal cohort study: HAVANA2 (HPV Amongst Vaccinated and Nonvaccinated Adolescents after 2-doses). Every year, vaccinated and unvaccinated participants filled out an online questionnaire and provided a vaginal self-sample for determination of HPV by the SPF10-LiPA25 assay, able to detect 25 HPV types including 12 high-risk (hrHPV) types. Type-specific incidence and persistence rates were calculated. VE against incident type-specific infections and pooled outcomes was estimated by a Cox proportional hazards model with shared frailty between the HPV types.

Results: A total of 2027 girls completed participation in the first year of the study, of whom 1098 (54.2%) were vaccinated according to a 2D schedule. Although HPV prevalence was low, the highest incidence rate of hrHPV types was observed for HPV51 among both vaccinated (5.0 per 1000 person-years) and unvaccinated participants (6.7 per 1000 person-years). Adjusted pooled VE against incident HPV16/18 infections was 81.0% (95% CI, 12.9-95.8%), and VE was 85.5% (95% CI, 34.7-96.8%) against cross-protective type infections (HPV31/33/45).

Conclusions: Four years post-vaccination, two doses of 2vHPV vaccination were highly effective in the prevention of incident HPV16/18 infections and additionally provided good cross-protection to HPV31/33/45. Our VE estimates rival those derived from birth cohorts eligible for routine 3D immunization, indicating comparable protection of 2D schedules. Although longer follow-up data is needed, the current findings are promising regarding clinical impact following a reduced dosing schedule.

#1569

5 - HPV prophylactic vaccines

Inflammation-related Adverse Reactions Following HPV Vaccination Indicate a Stronger Immune Response

Zhuang C[1], Wu T[2], Zhang J[3]

[1]STATE KEY LABORATORY OF MOLECULAR VACCINOLOGY AND MOLECULAR DIAGNOSTICS, XIAMEN UNIVERSITY, Xiamen, China

[2]State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, National Institute of Diagnostics and Vaccine Developme, Xiamen, China

[3]State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, National Institute of Diagnostics and Vaccine Developme, Xiamen, China

Background/Objectives: Vaccine hesitancy, especially the concern about vaccine safety or adverse reactions (AR), impede the implementation of vaccines. Unveiling the scientific basis of ARs is helpful for decreasing vaccine hesitance. Although it is a long tale that the stronger reactivity of a vaccine usually denotes a stronger immune response, few straightforward data from large-scale human trials was reported previously. In this study, we aimed to explore the relationship between adverse reactions that may be caused by inflammation and immune responses following vaccinations on the basis of data from the clinical trial of a bivalent HPV-16/18 vaccine (Cecolin®) licensed in China.

Methods: Cecolin® (Xiamen Innovax, Xiamen, China), an aluminum hydroxide adjuvant-absorbed recombinant Escherichia coli-produced vaccine, which has been proved safe, effective and to have seroconversion rates of 100% after three doses at month 0, 1 and 6, as described previously1-2. We used data from phase â...¢ clinical trial (NCT01735006) of Cecolin® with a total sample size of more than 2300 women aged 18-45 y who received a full course of the vaccine to analyze the correlationship between inflammation-related solicited adverse reactions (ISARs, including pain, redness, swelling or induration at the injection site and fever) following vaccinations and IgG antibodies at month 7.

Results: In the phase III trial of Cecolin®, more than 40% of vaccinees had at least once ISAR, whose geometric mean concentrations (GMCs) for IgG anti-HPV-16 and IgG anti-HPV-18 were significantly higher in participants with any ISAR following vaccination than in those without an ISAR ($P < 0.001$; see Supplementary Table 1). Furthermore, the severity and the number of injections resulting in ISARs also appear to be influencing factors for the levels of antibodies.

Conclusions: This study suggests strong evidence of a significant correlationship between ISARs and higher antibody levels after HPV vaccination. Inflammation may even be a prediction of successful immunization outcomes of HPV vaccines. The findings might provide a fundamental weapon to defense the vaccine hesitancy come from the common and tolerable adverse reactions such as fever and local pain.

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Supplementary Table 1

#2193

2 - Epidemiology and natural history

Monitoring the impact of HPV vaccination on cervical cancer in England: results from 2013-2017 diagnoses in females under 30 years of age

Milbourn H[1], Checchi M[2], Panwar K[3], Mesher D[4], Beddows S[5], Soldan K[6]

[1]Blood Safety, Hepatitis, STI and HIV Division, National Infection Service, Public Health England, London, United Kingdom

[2]PUBLIC HEALTH ENGLAND, London, United Kingdom

[3]Virus Reference Department, National Infection Service, Public Health England, London, United Kingdom

[4]PUBLIC HEALTH ENGLAND, London, United Kingdom

[5], London, United Kingdom

[6]Blood Safety, Hepatitis, STI and HIV Division, National Infection Service, Public Health England, London, United Kingdom

Background/Objectives: The national Human papillomavirus (HPV) Vaccination Programme began offering vaccination to females in England in 2008 and was extended to include males from 2019. Since its introduction, we have reported declines in HPV vaccine-type infection prevalence in females and anogenital warts incidence in both females and males as an early indication of the impact of the vaccination programme. The peak incidence of cervical cancer diagnoses occurs at ages 25-34 with relatively few diagnoses in under 25 year-olds. Females in routine vaccination cohorts are yet to reach this age group within the surveillance period. We present results from ongoing surveillance activities between 2013-2017 to monitor the impact of vaccination on cervical cancer incidence and on the distribution of high risk (HR) cancer causing HPV types, and to be vigilant for any sign of vaccine failure.

Methods: Residual biopsy tissue was requested from hospitals for females under 30 years of age diagnosed with cervical cancer between 2013-2017. Sections of biopsy material were tested for type-specific HPV DNA using an in-house multiplex PCR and Luminex-based genotyping test. Vaccination status was requested for individual patients from their general practitioner (GP).

Results: 80% of diagnoses, among women who would have been eligible for vaccination, occurred in women in older catch-up cohorts, first eligible for vaccination at 17/18 years old. Of the 362 requests sent for residual tissue, 81% were returned and tested for HPV DNA (N=293)(Table 1). A HR HPV type was detected in 95% of specimens (N=279). HPV16 or 18 was present in 85% of samples with HR HPV detected (N= 236). 6 biopsy specimens were returned from females in routine vaccination cohorts. HPV DNA was extracted from 2 but HR HPV was not detected in either.

Conclusions: Most cervical cancer diagnoses in women under 30, up to end of 2017, occurred in older vaccination cohorts where pre-existing HPV infection at time of vaccination is more likely and vaccine coverage was lower. Therefore, as expected, the proportion of cases with HPV 16/18 are similar to results prior to the introduction of the HPV Vaccination Programme. Substantial reductions in the proportions of cervical cancers positive for HPV 16/18 are expected in future years as females vaccinated at younger ages reach their mid-late 20s. Thus far, there has been no HR HPV infection detected in routine cohort diagnoses. Over the coming years this surveillance will be able to address any evidence of type-replacement or vaccine failure with precision as cervical cancer diagnoses continue to be monitored.

#2345

5 - HPV prophylactic vaccines

HPV National immunization programmes status in 53 WHO countries

Joura E[1], Faivre P[2], Bonanni P[3], Lopalco P[4], Begroth T[5], Varga S[6], Gemayel N[7], Drury R[8]

[1]Medical University of Vienna, Gynecology and Gynecologic oncology, Vienna, Austria

[2]Regional Market Access Europe, Lyon, France

[3]University of Florence, Health sciences, Florence , Italy

[4]University of Pisa, Health Sciences, Pisa, Italy

[5]Center for Observational and Real-world Evidence, MSD, Stockholm, Sweden

[6]MERCK AND CO., INC., Kenilworth, United States

[7]AMARIS Consulting & Innovation, HEMA (Health Economics & Market Access), Barcelona, Spain

[8]MSD FRANCE, Lyon, France

Background/Objectives: Since the introduction of HPV vaccination (HPVv), National immunization programmes in WHO Europe (WHO/ER) have rapidly evolved based on International and European recommendations. Several countries have recently decided to implement boys HPVv in addition to existing girls HPVv programmes. The objective of this research was to review the current status of recommendations, funding and program implementation of HPVv in WHO/ER.

Methods: A targeted literature review of WHO database and country websites (e.g. ministry of health, national authority) was conducted between August 2018-September 2019 across WHO/ER countries (n=53). Data included target HPVv population, vaccination schedule, setting (e.g. schools, healthcare center), and funding for primary (reported target-age group) and catch-up cohorts (individuals older than primary target-age). Funding was considered from patient's perspective. HPVv was considered fully-funded if patient had no out-of-pocket pay, partially-funded if patient had to pay for part of vaccination and no-funding if vaccination was fully paid by the patient.

Results: In WHO/ER, 85% of countries (n=45/53) had national recommendations for HPVv among which 80% (n=36/45), 4% (n=2/45) and 16% (n=7/45) of countries had fully-funded, partially-funded and no-funding programs for the primary cohort, respectively. Fully-funded or partially-funded HPVv programs were available for girls only and girls & boys in 61% (n=23/38) and 39% (n=15/38) of countries, respectively. For catch-up cohorts, fully-funded or partially-funded HPVv programs were available in 26% (n=14/53) of countries. In fully-funded or partially-funded HPVv countries, vaccination occurred in healthcare centers (n=15/38), schools (n=16/38) or both schools and healthcare centers (n=3/38); with missing information regarding 4 countries.

Conclusions: HPVv programs have been widely implemented in WHO/ER but 17 countries in the region still lack national recommendations and/or full funding. Substantial variations prevail across programmes including the target immunization population.

#2168

5 - HPV prophylactic vaccines

HUMAN PAPILLOMAVIRUS VACCINE EFFECTIVENESS BY NUMBER OF DOSES: UPDATED SYSTEMATIC REVIEW OF DATA FROM NATIONAL IMMUNIZATION PROGRAMS

Markowitz L[1], Drolet [2], Lemieux-mellouki P[3], Lewis R[4], Perez N[5], Brisson M[6]

[1]CENTERS FOR DISEASE FOR DISEASE CONTROL AND PREVENTION, Atlanta, United States

[2]Université Laval, Québec, Canada

[3]Université Laval, Québec, Canada

[4]Centers for Disease Control and Prevention, Atlanta, United States

[5]Université Laval, Québec, Canada

[6]Université Laval, Québec, Canada

Background/Objectives: Human papillomavirus (HPV) vaccines were first licensed as a 3-dose series; a 2-dose series is now recommended in some age groups. There are also data suggesting high efficacy with a single dose.

Methods: We updated a previous systematic literature review on HPV vaccine effectiveness in post-licensure observational studies that examined effectiveness by number of doses, using the same methods as in our previous paper. We searched Medline and Embase databases from January 1, 2007 through August 10, 2020 using prespecified criteria. Data were extracted from included articles and summarized in a narrative synthesis. We also conducted quality assessments of all papers for bias due to selection, information, and confounding.

Results: Of 6565 articles identified, 124 full articles were assessed and 32 included in our review (14 from our initial review and 18 from our update). All studies were conducted within the context of recommended 3-dose schedules of bivalent (6) or quadrivalent HPV vaccine (26) from 10 different countries. Eight evaluated effectiveness for prevention of HPV prevalence, 9 anogenital warts, and 15 cervical cytological or histological abnormalities. All investigators attempted to control for or stratify by potentially important variables, such as age at vaccination. Seven studies also evaluated impact of buffer periods (lag time) for case counting and 10 evaluated different intervals between doses for 2-dose vaccine recipients. Studies that stratified by age at vaccination found higher vaccine effectiveness with younger age at vaccination, although differences were not all formally tested. Among 29 studies that evaluated 3 doses, all found significant effectiveness, except 2 small studies among males. Among 28 studies that evaluated 2 doses, 17 found significant effectiveness, and among 30 studies that evaluated 1 dose, 16 found significant effectiveness in some or all analyses. More recent studies that adjusted or stratified analyses by age at vaccination found similar effectiveness with 1, 2, and 3 doses. All studies were judged to have moderate or serious risk of bias. Most biases would result in lower effectiveness estimated with fewer doses.

Conclusions: This updated systematic review of 32 studies found that highest effectiveness was reported with 3 doses in most studies; however, some found no statistically significant difference by number of doses. Moderate or serious risk of bias was found in all studies. Observational effectiveness studies, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias, could help inform vaccination policy.

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#2201

5 - HPV prophylactic vaccines

FREQUENCY OF SAFETY EVENTS OCCURRING ON THE DAY OF VACCINATION WITH 4-VALENT HUMAN PAPILLOMAVIRUS AMONG MALES

Amend K[1], Marks M[2], Turnbull B[3], Zhou L[4], Velicer C[5], Saddier P[6], Seeger J[7]

[1]OPTUM, Boston, United States

[2]MERCK, West Point, United States

[3]Optum, Boston, United States

[4]Optum, Boston, United States

[5]MERCK & CO., Kenilworth, Nj, United Kingdom

[6]MERCK & CO., INC., West Point, United States

[7]Optum, Boston, United States

Background/Objectives: The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine), Gardasil®, is indicated for the prevention of several HPV-related diseases. In the US, it was licensed for use in females in 2006 and males in Oct-2009. The 4vHPV vaccine is licensed in many parts of the world. The objective was to assess the frequency of pre-specified safety events that occur on the day of 4vHPV vaccination among males.

Methods: Within a US health insurance database, males receiving 4vHPV vaccine were identified. Syncope, epilepsy/convulsions, head trauma, and allergic new events associated with outpatient visit, emergency department visit or hospitalization occurring on the day of vaccination were identified using diagnostic codes. These events were pre-specified based on consideration of temporal and biological plausibility. Event rates (per 10,000 doses) were calculated and compared with those in males receiving a vaccine other than 4vHPV vaccine (Td/Tdap, hepatitis A, meningococcal, or influenza) matched on age and calendar time of vaccination. Separate analyses were conducted for all doses combined, Dose 1 only, and for those receiving concomitant vaccinations.

Results: Between Oct-2009 and Dec-2016, 202,737 4vHPV doses were administered to 114,035 males; 160,867 doses were matched to comparators. Thirty-one percent (31%) of 4vHPV vaccine recipients received a concomitant vaccine. In the all dose analyses of 4vHPV vaccinations vs. comparators, there were higher rates of allergic events (21.1, 95% CI: 18.9-23.4 vs. 11.4, 95% CI: 9.8-13.2), lower rates of epilepsy/convulsions (5.7, 95% CI: 4.6-7.0 vs. 7.6, 95% CI: 6.3-9.1) and similar rates of syncope and head trauma. Similar patterns were observed for Dose 1 only and by number of concomitant vaccinations.

Conclusions: Higher rates of allergic events observed in this study are consistent with the safety profile of 4vHPV vaccination established from previous studies/surveillance programs.

#1660

5 - HPV prophylactic vaccines

HPV VACCINATION EFFECTIVENESS WITHIN THE ANCONA CERVICAL SCREENING PROGRAMME: COHORT STUDY

Acuti Martellucci C[1], Morettini M[2], Flacco M[3], Giacomini G[4], Cimini D[5], Barbadoro P[6], Pasqualini F[7]

[1]Department of Biomedical Sciences and Public Health, University of the Marche Region, Ferrara, Italy

[2]Oncologic Screening Unit, Prevention Department, ASUR Marche, Jesi, Italy

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

[4]Oncologic Screening Unit, Prevention Department, ASUR Marche, Senigallia, Italy

[5]Infectious Diseases Prevention and Surveillance, Prevention Department, ASUR Marche Area Vasta 2 , Fabriano, Italy

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

[7]Oncologic Screening, Prevention Department, ASUR Marche Area Vasta 2 , Ancona, Italy

Background/Objectives: In Italy, HPV immunization is recommended since 2007 in adolescents, and organized cervical cancer screening programmes target women from age 25 years.1 In the Ancona area, women eligible for catch-up HPV immunisation have started entering the screening. Since evidence is still scarce on the population-level impact of HPV vaccination in the country,2 we aimed to assess its protective effectiveness against screen-detected cervical abnormalities.

Methods: ï»¿In a population-based cohort study, we included women residing in the Ancona area, born in 1990 through 1993 and screened between January 1st 2015 and June 30th 2020. Deterministic linkage was used to link vaccination and screening data from official healthcare registries. Logistic regression (adjusted for age, nationality, residence, and number of screening tests) was used to assess possible associations between vaccination with at least one dose, or three doses of the vaccine and the following four main outcomes: ASC-US+ and LSIL+ Pap smears, and CIN1+ and CIN2+ histology. Analyses were repeated applying six, twelve, and 24 months buffer periods.

Results: The overall sample included 4,665 women (mean age 26.6 years, SD 1.5), of which 1,118 (24.0%) were vaccinated with at least one dose. Overall, 265 (5.7%) women had ASC-US+ Pap smears, and 107 (2.3%) had LSIL+, while 70 (1.5%) had CIN1+ histology, and 35 (0.8%) had CIN2+. Compared to unvaccinated women, those vaccinated had a similar risk of ASC-US+ results. However, they had adjusted odds ratio (AOR) 0.55 (95% confidence interval - CI - 0.33 to 0.91; $p<0.05$) of LSIL+, AOR 0.43 (95% CI 0.22 to 0.86; $p<0.05$) of CIN1+, and AOR 0.31 (95% CI 0.11 to 0.91; $p<0.05$) of CIN2+. Findings were similar when applying six, twelve, and 24 months buffer periods.

Conclusions: In the context of an organised cervical screening programme in Italy, observed effectiveness of catch-up HPV vaccination was 45% against LSIL+, and 69% against CIN2+. The similar risk of ASC-US+ in the vaccinated and unvaccinated women confirms the inadequacy of Pap smear for screening young vaccinated women, and the findings ultimately support the recommendation to start screening vaccinated women from an older age.3

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FC12 - Management II

#2214

22 - Diagnostic procedures / management

ADHERENCE TO FOLLOW-UP AFTER NON-NEGATIVE HPV-TESTS AMONG WOMEN AGED 60-64 AND THE ASSOCIATED RESOURCE USE: A REGISTER-BASED COHORT STUDY

Joergensen S[1], Andersen B[2], Petersen L[3], Rebolj M[4], Njor S[5]

[1]Department of Public Health Programmes, Randers Regional Hospital; Department of Clinical Medicine, Aarhus University, Randers, Denmark

[2]AARHUS UNIVERSITY, Randers, Denmark

[3]Open, Odense University Hospital. Gynecology and Obstetrics, Southern Denmark University, Odense, Denmark

[4]Cancer Prevention Group, School of Cancer & Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King's C, London, United Kingdom

[5]Department of Public Health Programmes, Randers Regional Hospital; Department of Clinical Medicine, Aarhus University, Randers, Denmark

Background/Objectives: Human papillomavirus (HPV) testing is more sensitive for the detection of high-grade cervical intraepithelial neoplasia. In Denmark before 2021, HPV testing was used only for women aged 60-64. After a negative primary screening test, women were discharged from further cervical cancer screening. Women with a positive HPV test were referred to colposcopy (if they had abnormal cytology or were infected with HPV16/18) or for a new test in 12 months. This study investigated the adherence to the recommended follow-up after a positive HPV test, the overall resource use during this follow-up, and whether any organizational or individual factors affected the observed patterns.

Methods: We included all 2,924 women aged 60-64 years who received a positive or an inadequate screening result when attending primary HPV screening between March 2012 and the end of 2016. These women were observed through their pathway of follow-up. All relevant follow-up tests and procedures were retrieved from the highly complete Danish health registers, and the data were linked at the individual level. We estimated the total numbers of tests and diagnostic procedures utilised during the follow-up, and determined to what extent the patterns followed the national recommendations for follow-up. We also studied the association between follow-up adherence and the women's region of residence, type of health provider, and history of screening abnormalities.

Results: Preliminary results show that, overall, 94% of HPV-positive women had some follow-up. To a great extent, the patterns diverged from the recommendations. We observed that some of the follow-up patterns were of a local nature, and that often, the re-testing was done either too early or too late compared to what was recommended. Among women with inadequate HPV screening tests, 44% were re-tested on time. Among women referred to colposcopy, 82% of women attended on time. These patterns will be reported in detail at the conference.

Conclusions: With our comprehensive mapping of the real-life follow-up patterns among women with abnormal primary HPV screening, we found that the patterns often diverged from the recommendations. Addressing inconsistencies in follow-up should help to improve the screening programs and secure an equal and reliable follow-up care service for all women.

#2204

23 - Colposcopy

CLINICAL MANAGEMENT OF OLDER POSTMENOPAUSAL WOMEN REFERRED FOR COLPOSCOPY DUE TO AN ABNORMAL SCREENING TEST

Gustafson L[1], Tranberg M[2], Christiansen A[3], Lapirtis H[4], Krogh L[5], Hjorth I[6], Hammer A[7], Booth B[8]

[1]Department of Clinical Medicine, Aarhus University, Denmark and Department of Public Health Programmes, Randers Regional Hospita, Randers, Denmark

[2]RANDERS REGIONAL HOSPITAL, Randers , Denmark

[3]Department of Obstetrics and Gynecology, Gødstrup Hospital, Gødstrup, Denmark

[4]Department of Obstetrics and Gynecology, Randers Regional Hospital, Randers, Denmark

[5]Department of Obstetrics and Gynecology, Viborg Regional HospitalDepartment of Obstetrics and Gynecology, Viborg Regional Hospit, Viborg, Denmark

[6]Department of Obstetrics and Gynecology, Horsens Regional Hospital, Horsens, Denmark

[7]Department of Obstetrics and Gynecology, Gødstrup Hospital and Department of Clinical Medicine, Aarhus University, Gødstrup, Denmark

[8]Department og Gynaecology and Obstetrics, Randers Regional Hospital, Randers, Denmark

Background/Objectives: Background: In older postmenopausal women, performance of colposcopy is often inadequate due to the retraction of the transformation zone into the cervical canal. This challenges the colposcopic examination and the collection of adequate cervical punch biopsies. Consequently, the "true" incidence of cervical precancer among older women may be underestimated and may explain the observed discrepancy between incidence rates of cervical precancer and cervical cancer at older ages. The aim of this study was to describe the clinical management of Danish women aged 69+ who had been referred for colposcopy due to an abnormal screening test.

Methods: Methods: We conducted a cohort study from January 2017 through December 2020. We included women who had been referred to gynecology departments in Central Denmark Region due to an abnormal screening test during 2017 (~200 women). Women were eligible if they were born before 1948 and had been invited for an additional HPV-based screening test. Women were excluded if smears had been obtained as part of follow-up due to previous abnormal screening tests. Information on colposcopic findings, behavioral risk factors, screening history, and results of subsequent cervical smears and biopsies until end of follow-up in December 2020 were collected from medical records and the Danish Pathology Databank. Results will mainly be reported descriptively, and chi2 and Fishers exact test will be used for comparison, as appropriate.

Results: Results: Results will be presented at Eurogin 2021.

Conclusions: Conclusion: This study will provide new and important evidence on how to clinically manage older postmenopausal women with abnormal screening tests, while balancing risk of underdiagnosis versus risk of overtreatment. Additionally, our results may help identify areas of particular interest where more research is needed.

#2191

23 - Colposcopy

Colposcopy impression has a key role in the estimation of the risk of HSIL/CIN3

Del Pino M[1], Martí C[2], Angeles M[3], Munmany M[4], Rakislova N[5], Ordi J[6], Torné A[7]

[1]HOSPITAL CLINIC DE BARCELONA, Barcelona, Spain

[2]Gynecology Oncology Unit. Hospital Clínic Barcelona, Barcelona, Spain

[3]Gynecology Oncology Unit. Hospital Clínic Barcelona, Barcelona, Spain

[4]Gynecology Oncology Unit. Hospital Clínic Barcelona, Barcelona, Spain

[5]Department of Pathology, Hospital Clínic Barcelona, Barcelona, Spain

[6]Department of Pathology, Hospital Clínic Barcelona, Barcelona, Spain

[7]Gynecology Oncology Unit. Hospital Clínic Barcelona, Barcelona, Spain

Background/Objectives: Recently published international guidelines for cervical cancer screening highlight the need for adjusting the management of women according to their individual risk of precancer and propose a risk-based algorithm . However, these guidelines consider only the screening test results for risk-estimation, whereas it has been clearly shown that colposcopy examination provides key information on the risk of harboring cervical cancer precursors . Indeed, it has been suggested that the risk that each particular woman has of harboring a precancer can be better estimated by combining the results of the three tests (Pap smear, hrHPV testing and colposcopy impression). We aimed to analyze the value of adding colposcopy impression to screening tests for the diagnosis of HSIL/CIN3.

Methods: This was a prospective study conducted in the Colposcopy Unit of the Hospital Clínic of Barcelona from January 2014 to September 2015. 302 women referred to colposcopy due to an abnormal Pap smear were included. All women underwent hrHPV detection and genotyping (HPV 16/18 vs. non 16/18 hrHPV), and colposcopy with at least one biopsy. Since risk estimates for HSIL/CIN3 are much less heterogeneous than HSIL/CIN2+ results, women with HSIL/CIN3 (including patients with a histological diagnosis of HSIL/CIN3 or adenocarcinoma in situ) were also segregated in the analysis and considered as the main end-point of the study. For risk estimation, "high-risk" results included either a HSIL result in Pap smear, and/or HPV 16/18 infection, and/or grade 2 findings in the colposcopy impression. "Low-risk" included a <HSIL Pap smear result, a negative result for HPV 16/18 and colposcopy not showing grade 2 findings.

Results: HSIL Pap smear, HPV 16/18 and grade 2 colposcopy findings increased the risk of HSIL/CIN3 in the univariate analysis but only colposcopy retained significance in the multivariate model. Figure 1 shows the prevalence of HSIL/CIN3 and HSIL/CIN2+ according to the combined results of the tests in the 231 women in whom the absence of grade 2 colposcopy findings could be confidently excluded (women with a type 1 or 2 transformation zone and women with a type 3 transformation zone with grade 2 findings). There was a correlation between the results of the tests and the risk of harboring histological HSIL/CIN3 (red triangles). At least 30% of the women with grade 2 colposcopy findings had HSIL/CIN3, independently of the screening test results. Among women with an HSIL Pap smear and grade 2 colposcopy findings, 53.3% had HSIL/CIN3 independently of the hrHPV genotype. Contrarily, the prevalence of HSIL/CIN3 in women with <HSIL Pap smear, non HPV 16/18 infection and normal colposcopy or with grade 1 findings was 2.9% and 8.1%, respectively. Remarkably, the correlation for the combined results of the tests and the prevalence of HSIL/CIN2+ (black diamon) was much lower.

Conclusions: In conclusion, the results of our study highlight the essential role of colposcopy in identifying women with abnormal screening test results at high risk for underlying HSIL/CIN3. The addition of colposcopy impression can refine the management of women with abnormal screening test results to avoid missing HSIL/CIN3 lesions without overtreating an unacceptable number of patients.

References: Silver MI, Andrews J, Cooper CK, et al. Risk of Cervical Intraepithelial Neoplasia 2 or Worse by Cytology, Human Papillomavirus 16/18, and Colposcopy Impression: A Systematic Review and Meta-analysis. Obs Gynecol. 2018;132(3):725-735. doi:10.1097/AOG.0000000000002812 Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2017;370(9590):890-907. doi:10.1016/S0140-6736(07)61416-0 Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. 2020;24(2):102-131. doi:10.1097/LGT.0000000000000525 Egemen D, Cheung LC, Chen X, et al. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. 2020;24(2):132-143. doi:10.1097/LGT.0000000000000529 Cheung LC, Egemen D, Chen X, et al. 2019 ASCCP Risk-Based Management Consensus Guidelinesâ€¯: Methods for Risk Estimation , Recommended Management , and Validation. 2020;24(2):90-101. doi:10.1097/LGT.0000000000000528 Schiffman M, Wentzensen N, Perkins RB, Guido RS. An Introduction to the 2019 ASCCP Risk-Based Management Consensus Guidelines. 2020;24(2):87-89. doi:10.1097/LGT.0000000000000531 Farnsworth A, Roberts JM, Garland SM, Crescini J, Kaldor JM, Machalek DA. Detection of high-grade cervical disease among women referred directly to colposcopy after a positive HPV screening test varies with age and cytology findings. Int J Cancer. 2020;(May):1-8. doi:10.1002/ijc.33128 Wentzensen N, Walker J, Smith K, et al. A prospective study of risk-based colposcopy demonstrates improved detection of cervical precancers. Am J Obstet Gynecol. 2018. doi:10.1016/j.ajog.2018.02.009

Figure 1

#1939

23 - Colposcopy

Assisted Digital Cervicoscopy ADC The modern gynecologic examination.

Djaoui R[1]

[1]Israel Colposcopy Center, ,, Israel

Background/Objectives: 8/01/2021 ASSISTED DIGITAL CERVICOCOPY (ADC) THE MODERN GYNECOLOGIC EXAMINATION. 1- Evolution of gynecologic examination: Colposcopy, Pap test, HPV testing, vaccination and recent importance of the vaginal microbiota which can explain regression or progression of cervical cancerisation. 2- Two kinds of cervix examination: (according to Fernand COUPEZ France). - Classical colposcopy: Examination by specialists using heavy and expensive material. Possible psychologic consequences. - Assisted Digital Cervicoscopy: Routine examination of the cervix for all gynecologists.

Methods: 3- MobileODT: New tool, new approach. Easy, mobile, and sophisticated. (Ref. our communication at Eurogin 2018 Lisbon).

Results: 4- Few images taken with MobileODT: ASCUS, CIN, Vaginal infection and microbiota.

Conclusions: CONCLUSION: - Importance of routine Assisted Digital Cervicoscopy. - In case of vaginal infection do not start by Paptest but vaginal sample and treatment according to the result. After treatment. Pap, biopsy and follow up. - Revise the decisional algorithms.

#2044

24 - Cervical neoplasia

CERVICAL CONIZATION BETWEEN 2013 AND 2018 IN WOMEN 18 TO 45 YEARS OLD - RESULTS FROM A GERMAN STATUTORY HEALTH INSURANCE CLAIMS DATA ANALYSIS

Reuschenbach M[1], Stephan A[2], Prabhu V[3], Wölle R[4], Saxena K[5], Jacob C[6], Schneider K[7], Schneider A[8], Greiner W[9], Hampl M[10]

[1]Global Medical and Scientific Affairs, MSD Sharp & Dohme GmbH DOHME GmbH, Haar, Germany

[2]Department of Market Access, MSD SHARP & DOHME GmbH, Haar, Germany

[3]MERCK & CO., INC, Kenilworth, United States

[4]Department of Market Access, MSD SHARP & DOHME GmbH, Haar, Germany

[5]Center for Observational and Real-World Evidence (CORE), Merck & Co., Inc., Kenilworth, Nj, United States

[6]Xcenda GmbH, Hannover, Germany

[7]Xcenda GmbH, Hannover, Germany

[8]Xcenda GmbH, Hannover, Germany

[9]DEPARTMENT OF HEALTH ECONOMICS AND HEALTH CARE MANAGEMENT, BIELEFELD SCHOOL OF PUBLIC HEALTH, Bielefeld, Germany

[10]UNIVERSITY HOSPITAL OF DÜSSELDORF, Düsseldorf, Germany

Background/Objectives: Cervical intraepithelial neoplasia (CIN) can develop from persistent human papillomavirus (HPV) infections. Cervical conization, such as loop electrosurgical excision (LEEP), is a commonly performed surgical procedure in women for treatment of high-grade CIN. The objective of this study was to estimate the annual proportion of women 18-45 years-old undergoing cervical conization in Germany between 2013 and 2018.

Methods: This was a retrospective cross-sectional claims data analysis using the Institute for Applied Health Research Berlin (InGef) Research Database, which covers approximately 4 million lives and is representative for the German population regarding age and gender. Annual proportions of women undergoing cervical conization were determined as number of eligible women (aged 18-45 years old and observable throughout the respective calendar year, except for women who deceased) with a recorded claim for cervical conization (OPS code 5-671.0* or 5-671.1*) in each calendar year divided by the total number of eligible women in the respective year in the database.

Results: We identified 1,531, 1,532, 1,542, 1,425, 1,288 and 1,322 women at the age of 18-45 undergoing cervical conization in 2013, 2014, 2015, 2016, 2017, and 2018, respectively. The overall annual proportion of women aged 18 to 45 years undergoing cervical conization was 2.4/1,000 in 2013 and 2.1/1,000 in 2018. Women aged 31-35 accounted for 27.0% and 32.2% in 2013 and 2018, respectively, of those undergoing conization, and had also the highest rate of conization from 2014-2018 compared to the other age groups. Women aged 20-26 years-old accounted for 16.1% and 8.3% in 2013 and 2018, respectively, of those undergoing conization. Over 60% of all observed claims for cervical conizations were recorded in women aged 31-45 years from 2013 (62.3%) to 2018 (72.8%) which reflects an increase of 10.5% points from 2013 to 2018.

Conclusions: The burden of conizations remains substantial particularly in women over the age of 30. Reasons for the observed changes in younger age groups were not assessed but could be due to more reluctant indication for conization in the more recent years or decreases in diagnoses of CIN2+, which may be driven by changes in behavior and screening patterns. Also, HPV vaccination of the younger age groups might have had an impact. Vaccination was recommended and funded for 12-17 years old girls from 2007-2014 in Germany, after 2014 for 9-14 year-olds with catch-up to 17, since 2018 including boys. Interventions to prevent CIN2+ and conizations remain important, also in women over the age of 30.

#1866

24 - Cervical neoplasia

A PHASE 3 MULTICENTER, DOUBLE BLIND, PROSPECTIVE, RANDOMIZED, PLACEBO CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF CEVIRA® IN PATIENTS WITH CERVICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL)

Chen F[1], Hillemanns P[2], Zhang M[3]

[1]Department of Obstetrics and Gynaecology, Peking Union Medical College Hospital, Beijing, China

[2]HANNOVER MEDICAL SCHOOL, DEPARTMENT OF GYNAECOLOGY AND OBSTETRICS, Hannover, Germany

[3]Asieris Pharmaceuticals, Shanghai, China

Background/Objectives: HSIL (CIN2, 3) is generally managed by removing or destroying the abnormal cervical tissue, using excision (e.g., loop electrosurgical excisional procedure (LEEP), cold knife conization) or ablation treatment modalities. Current treatment methods may carry risk of vaginal cramping, discharge, bleeding, and infections. LEEP is also associated with increased risk of preterm delivery. Due to the untoward side effects, particularly the risk for future pregnancies, there is an unmet medical need of non-surgical treatment for HSIL, especially for young women of reproductive age. Cevira® for vaginal use is an investigational photodynamic therapy (PDT) product currently being developed as a non-surgical treatment for HSIL. It contains a drug ointment and an integrated device for drug delivery and light illumination. The Cevira® product is administered vaginally to the cervix by a gynecologist. The patient is free to resume normal daily activities immediately after administration. After treatment, the device is removed by the patient. The treatment preserves the underlying stroma and thereby the competence of the cervix, avoiding the side effects associated with surgical procedures. A phase 2b study1 has shown encouraging efficacy and safety results for Cevira®. The objective of this phase 3 trial is to evaluate the efficacy and safety of Cevira®compared to placebo in treatment of patients with cervical histologic HSIL.

Methods: The study is designed as a double blind, prospective, randomized, placebo controlled, multi-center study in patients with an adequate colposcopy and histology diagnosis of HSIL. Patients will be randomized to Cevira® or placebo (2:1). Inclusion will be based on histology diagnosis determined by a panel of three pathological experts from a central laboratory in each region (China, and Europe). The randomization will be stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+, or HPV18+Oth+). The primary endpoint is the proportion of responders at 6 months after first treatment; a responder is defined as follows: normal histology, or LSIL histology and clearance of baseline HPV. Patients will receive one or two treatments; a second treatment will be administered in patients who at 3 months have a cytology of LSIL or more severe (HSIL). The re-treatment visit should be within 1 month of the three-month assessment visit. All patients will have an assessment visit at 6 months for primary efficacy and safety evaluation. All patients in the active treatment group will be followed for an additional 6 months in an open-label extension of the study. Additional efficacy and safety data will be collected at 12 months. Safety (adverse events) will be assessed at treatment visit(s), and at the 3, 6 and 12-month assessment visits. A total of 384 subjects will be enrolled in China and Europe. This trial is currently enrolling patients.

Results: Not available. This trial is currently enrolling patients.

Conclusions: Not available. This trial is currently enrolling patients.

References: Hillemanns P, Garcia F, Petry KU, Dvorak V, Sadovsky O, Iversen O, Einstein MH. A randomized study of hexaminolevulinate photodynamic therapy in patients with cervical intraepithelial neoplasia 1/2. Am J Obstet Gynecol. 2015 Apr;212(4): 465.e1-7.

#1397

7 - Immunotherapy - Immuno-oncology - New treatments

EFFICACY OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HIGH-RISK HPV INFECTED PATIENTS: RESULTS OF DIFFERENT STUDIES

Cortés J[1], Dexeus D[2], Palacios S[3], Serrano L[4], Clara G[5], Marín E[6], Miniello G[7], Riera M[8], Gaslain Y[9]

[1]Private Practice, , Spain

[2]Women's Health Institute, Barcelona, Spain

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

[4]Centro Médico Gabinete Velázquez, Madrid, Spain

[5]Hospital Materno Infantil Teresa Herrera, , Spain

[6]Hospital Alvaro Cunqueiro, Vigo, Spain

[7]Private Practice, Bari, Italy

[8]Institut Català de la Salut, Barcelona, Spain

[9]Procare Health Iberia, Barcelona, Spain

Background/Objectives: To evaluate the consistency of the efficacy of a non-hormonal multi-ingredient Coriolus versicolor-based vaginal gel, Papilocare®, on HPV clearance in patients infected by high-risk HPV (HR-HPV) in several studies.

Methods: Results at 6 months from independent observational non-comparative studies carried out in three different public centers and in a one private center were compared to results from both a randomized, open, parallel and controlled clinical trial comparing the Papilocare® vs wait and see approach (The Paloma RCT) and a observational, multicenter, prospective, one-cohort study (Papilobs real-life study). Two prospective (Vigo and Bari studies) and two retrospective studies (Coruña and Hospitalet studies) have been performed. Vigo study: HPV clearance of 25 patients infected by HPV 16 and/or 18 was evaluated as a secondary endpoint. Bari study: HPV clearance of 98 HR-HPV patients was evaluated as primary endpoint. Coruña study: 57 medical records of patients with HR-HPV were analyzed. HPV clearance was evaluated as primary endpoint. Hospitalet study: Data of 91 HR-HPV patients were evaluated. Primary endpoint: composite efficacy variable (percentage of patients with normal cytology and/or HPV clearance). Papilobs study: Interim data of 148 HR-HPV patients is presented. HR-HPV clearance was evaluated as secondary endpoint. Paloma RCT: 66 HR-HPV patients were evaluated. Percentage of patients with HR-HPV clearance was assessed as a secondary endpoint.

Results: After the 6-month treatment period, 48% and 57% of patients cleared HPV 16-18 and HR-HPV in Vigo and Bari studies, respectively. A reduction of 58% was observed in number of HR-HPV patients (Coruña) and 72.5% of patients negativized cytology and/or cleared HR-HPV (Hospitalet) ($p \leq 0.0001$ vs baseline for all results, Chi-square). In the Paloma RCT, HR-HPV clearance was observed in 63% of patients treated with Papilocare® vs 40% in the control group. Similar rate of 59% HR-HPV clearance was observed in the interim analysis of the Papilobs study.

Conclusions: Papilocare® has shown significant and consistent rates of HR-HPV clearance ranging from 50% to 70% in the 6 different studies. This high consistently rate of HR-HPV clearance should be further confirmed in ongoing studies.

FC14 - Public Health

#2395

38 - Public health

Decision making process of intent to receive COVID-19 vaccination relates to HPV vaccination receipt among young adults in Mountain West region of the United States

Kepka D[1], Chang E[2], Lipscomb J[3], Hill J[4], Mann S[5], Hashibe M[6], Christini K[7]

[1]HUNTSMAN CANCER INSTITUTE AND UNIVERSITY OF UTAH , Salt Lake City, United States

[2]University of Utah , Salt Lake City, United States

[3]Huntsman Cancer Institute and University of Utah, Salt Lake City, United States

[4]Huntsman Cancer Institute and University of Utah, Salt Lake City, United States

[5]Huntsman Cancer Institute and University of Utah , Salt Lake City, United States

[6]Huntsman Cancer Institute and University of Utah , Salt Lake City, United States

[7]Huntsman Cancer Institute and University of Utah , Salt Lake City, United States

Background/Objectives: To assess similarities and differences between receipt of the HPV vaccine and intention to receive the COVID-19 vaccine among young adults by demographic factors in the Mountain West of the U.S.

Methods: An online, self-administered, cross-sectional survey was conducted in two waves during October and December 2020 that included young adults ages 18-26 years old who live in rural and urban communities in the Mountain West region of the U.S. Participants were recruited through university, public health, and community list servs (N=925). The questionnaire asked participants to provide information on their demographics; general vaccination trust; HPV and HPV vaccination knowledge, and receipt of the vaccine; and COVID-19 questions about testing, concerns, and vaccination intentions. We hypothesized that a difference in COVID-19 vaccination intention between those who had received an HPV vaccination or not would be found and expected that the decision making process for getting the HPV vaccine and the COVID-19 vaccine are similar. HPV vaccination was self-reported. Participants were asked "When a COVID-19 vaccine becomes approved and available do you plan to get vaccinated?" Directed acyclic graphs informed selection and identified scientifically meaningful covariates for our model. Chi-square and penalized binary multivariate logistic regression was utilized.

Results: After controlling for the effect of gender, age, ethnicity, health insurance, frequency of religious services, month of survey, and prior COVID-19 testing, the odds of young adults who had received any HPV vaccination stating that they intended to get COVID-19 vaccinated was 1.9 times that of those who had not had any doses of the HPV vaccine. Pearson $\chi 2$ and unadjusted model estimates indicated that increasing time (i.e., month of survey) (p= 0.01, cOR=1.50, 95% CI=1.09-2.08), having received any HPV immunizations (p= 0.004, cOR=1.54, 95% CI=1.15-2.08), and having had a prior COVID-19 test (p=0.0063, cOR=1.53, 95% CI=1.13-2.07) were statistically significant factors of intent to obtain a COVID-19 vaccination. After model adjustments (for gender, age, ethnicity, health insurance, and frequency of religious services in addition to month of survey, HPV vaccination, and a prior COVID-19 test), male gender, younger age (18-20 years old), taking the survey in December, and having had an HPV vaccination were of statistical significance (aOR=1.88, 95% CI=1.27-2.84; aOR=1.67, 95% CI=1.15-2.44; aOR=1.87, 95% CI=1.25-2.83; and aOR=1.71, 95% CI=1.24-2.35, respectively).

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

References: References: DAG modeled using Daggity.net. Judea Pearl, Madelyn Glymour, and Nicolas P Jewell. Causality Inference in Statistics: A Primer. Wiley, New York, NY, USA. 1st edition, 2016.

#2400

38 - Public health

PERCEPTIONS ON REASONS FOR PAP AND HPV TESTING AMONG HEALTHCARE PROVIDERS IN FINLAND

Makkonen P[1], Anttila A[2], Heinävaara S[3], Sarkeala T[4], Sarvilinna N[5], Nieminen P[6], Virtanen A[7]

[1]The Finnish Cancer Registry, Espoo, Finland

[2]The Finnish Cancer Registry, Helsinki, Finland

[3]The Finnish Cancer Registry, Helsinki, Finland

[4]The Finnish Cancer Registry, Helsinki, Finland

[5]Faculty of Medicine,University of Helsinki, Finland, Helsinki, Finland

[6]Department of Obstetrics and Gynecology, Helsinki University Hospital, Finland, Espoo, Finland

[7]Department of Pathology, University of Helsinki and HUSLAB, Helsinki University Hospital, Finland, Espoo, Finland

Background/Objectives: In Finland an extensive opportunistic screening practice that concentrates especially on younger women exists alongside the national screening program. Awareness of the attitudes and perceptions on cervical cancer screening by healthcare providers is essential for assessing procedures to improve the current screening practice. Aim of the study is to assess healthcare providers' perceptions on indications for Pap- and HPV-testing. The eventual aim is to reduce unnecessary screening and enhance adherence to cervical cancer screening guidelines.

Methods: An anonymous electronic survey was conducted during spring 2018 among approximately 3000 healthcare providers in Finland. Healthcare providers' attitudes, beliefs, knowledge and practices on cervical cancer screening related topics were asked were asked. The target group were doctors, nurses, midwifes and laboratory personnel in the public primary, student and private healthcare and gynecology units in the secondary and tertiary healthcare. Questions asked were scored and significant perceptions and knowledge of national screening programme and guidelines were observed. Distribution of scores was analyzed by education, place of work, region and referring or not referring to Pap test.

Results: 531 health care professionals attended the survey. 97 % of the respondents knew there is a national screening program for cervical cancer and 61 % knew about the national EBM-based guidelines. 84 % of the respondents believed they knew at what age women are invited for screening, but actually 48 % knew the correct answer. There also seems to be confusion regarding the concept and indications for a pap or HPV-test. 47 % of the respondents considered that the first pap test in a screening purpose should be taken a few years after the first sexual intercourse. 70 % considered HPV-test should be used as a screening test, 27.8 % of them regarding HPV-test applicable for screening women aged under 30 years. Distribution of scores will be presented.

Conclusions: There are discrepancies in the perceptions of health care professionals with information available on natural history, evidence of benefits and harm, and current clinical guidelines on cervical screening services. Our study will likely give important information to determine procedures to intervene in the current screening practice.

#2402

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KNOWLEDGE AND AWARENESS ABOUT HUMAN PAPILLOMAVIRUS AND VACCINATION AGAINST IT AMONG ADOLESCENTS AND PARENTS IN LATVIA

Upmale A[1], Vanaga A[2], Rezeberga D[3], Zodzika J[4]

[1]RÄ«ga StradiÅ†Å¡ University, Faculty of Medicine, Latvia, Riga, Latvia

[2]RÄ«ga StradiÅ†Å¡ University, Faculty of Medicine, Latvia, Riga, Latvia

[3]RÄ«ga StradiÅ†Å¡ University, Departments of Obstetrics and Gynecology, Latvia, Riga Maternity hospital, Latvia, Riga East , Riga, Latvia

[4]Riga Stradins University, Department of Obstetrics and Gynaecology; Riga East Clinical University Hospital, Riga, Latvia

Background/Objectives: Immunization against human papillomavirus (HPV) in Latvia started in 2010. Since then, the average coverage is still under 60%. A lack of knowledge can seriously threaten the vaccination coverage, therefore understanding the acceptability of the HPV vaccination is critical. The aim of this study was to evaluate adolescents and parents' knowledge and their beliefs and awareness about HPV and vaccination.

Methods: A cross-sectional survey was carried out. Structured questionnaires were used for surveys in the Internet and in schools. 1576 questionnaires were analyzed. The age of respondents was 13 - 15 for adolescents, 28 - 60 for parents. Vaccinated and non-vaccinated adolescents and 12-17 year old child's parents were compared. Knowledge was assessed using 17 questions, overall knowledge was scored according to the correctly answered questions. This research was approved by the RSU Ethics Committee. The results were statistically analyzed using IBM SPSS 26.

Results: The study included 1266 adolescents (58.1% girls, 41.9% boys) and 310 parents (96.8% mothers, 3.2% fathers). 16.1% (n=204) of adolescents and 36.8 % (n=114) of parents said that their child is vaccinated against HPV. Using a scale from 1 to 5 correspondingly, on how informed they felt about HPV vaccine benefits and possible risks, the analysis indicated the mean 2.1 for adolescents and 3.5 for parents. 6.6% adolescents and 56.8% parents knew HPV may cause cervical cancer. The most common reason not to vaccinate for adolescents in 47.7% (n=630) was not knowing about the HPV vaccine. 18% (n=68) parents did not vaccinate their children because they thought the vaccine has many side effects. The main information source of HPV for parents in 26.3% (n=170) was the internet, in 25.1% (n=162) - the child's general practitioner. The parents of vaccinated children were statistically significantly more likely to have the child's general practitioner as a source of information ($p<0.001$). 54.5% adolescentsbelieved that most sexually active people do not develop HPV in their lifetime. 34.4% adolescents and 25.2% parents assumed that after the vaccination there is a risk of infertility. The knowledge score of the parents of vaccinated adolescents was statistically significantly higher than of the parents of non-vaccinated adolescents, the same was observed between vaccinated and non-vaccinated adolescents ($p<0.001$).

Conclusions: The study implies that the lack of knowledge about HPV and misconceptions about the vaccine and its benefits for health is the main reason for not to vaccinate. To increase the vaccination coverage, it is important to improve adolescents and their parents' knowledge.

#2284

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INVESTIGATING THE DECREASE IN PARTICIPATION IN THE DUTCH CERVICAL CANCER SCREENING PROGRAMME

Aitken C[1], Kaljouw S[2], Siebers A[3], Bron M[4], Morssink A[5], Van Kemenade F[6], De Kok I[7]

[1]ERASMUS MC UNIVERSITY MEDICAL CENTER, Rotterdam, Netherlands

[2]ERASMUS MEDICAL CENTER , Delft, Netherlands

[3]PALGA Foundation, Houten, Netherlands

[4]BEVOLKINGSONDERZOEK NOORD, , Netherlands

[5]Bevolkingsonderzoek Oost, Deventer, Netherlands

[6]Erasmus MC University Medical Center, Rotterdam, Netherlands

[7]Erasmus MC University Medical Center, Rotterdam, Netherlands

Background/Objectives: Declining attendance in the Dutch cervical cancer screening programme was recently observed, coinciding with preparations for implementation of primary hrHPV-based screening in January 2017. The switch to hrHPV-based screening involved many changes, including the type of tests offered (self-sampling or clinician-collected samples) and standardisation of invitation policies. We aimed to investigate which factors (personal and organisational) were related to attendance and whether these factors could explain the decrease in attendance.

Methods: We conducted a population-based cohort study including all women aged 30 to 60 years who were eligible for screening in the Dutch cervical cancer screening programme between 2014 and 2018. Attendance was defined as participation in the screening programme within 15 months of the start of the invitation-eligible year. We used data from Dutch nationwide network and registry of histo- and cytopathology (PALGA) linked with data from Statistics Netherlands to investigate population characteristics (position in the household, household income, socio-economic status, number of people in the household, migration background, age) and data from all five inviting organisations (called SO 1 to 5) to investigate the effect of cessing invitation by general practitioners (GPs). To control for the fact that invitation and reminder policies were directly related to SO between 2014 and 2016, we calculated one model per SO.

Results: Attendance rates varied by demographic and organisational characteristics. Compared to other groups within the same demographic or organisational covariate, higher attendance rates were observed in women who were employed (attendance rate: 60.8%), married (62.9%), Dutch (61.2%), in the highest income bracket (63.4%), living in households with four persons (65.3%) and women who were invited by their GP (69.8%). These patterns were observed in all five SOs. Differences in personal characteristics did not explain the decline in attendance rates. By adjusting for whether the GP or the SO sent the invitation, the differences in attendance rates between 2014-2015 and 2016 and between 2014-2015 and 2017-2018 were explained in some screening organisations.

Conclusions: Removing the possibility for GPs to send invitations explains some of the decline in participation, although this did not account for the total change in attendance. Variation in attendance by demographic characteristics highlights the need for targeted communication and invitation policies to encourage participation in underscreened groups.