Ed's List
May 2022

In The Know

Gyn Onc Literature of Significance

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Prepared by Ed Pavlik (Ed's List) --- University of Kentucky Medical Center *

Novel Coronavirus Information (OPEN ACCESS) https://www.elsevier.com/connect/coronavirus-information-center Expert guidance and commentary hosted by Elsevier and JAMA **(https://jamanetwork.com/journals/jama/pages/coronavirus-alert)**
https://academic.oup.com/jnci/article/113/1/1/5859629

New!!! GYN ONC Garage-a look under the hood. https://youtu.be/DpUBq73On0w

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May

Nucleosome footprinting in plasma cell-free DNA for the pre-surgical diagnosis of ovarian cancer. A Vanderstichele, P Busschaert, C Landolfo, S Olbrecht, A Coosemans, W Froyman, L Loverix, N Concin, E Ioana Braicu, P Wimberger, E Van Nieuwenhuysen, SN Han, T Van Gorp, T Venken, R Heremans, P Neven, T Bourne, B Van Calster, D Timmerman, D Lambrechts & I Vergote. npj Genom. Med. 7, 30 (2022). https://doi.org/10.1038/s41525-022-00300-5

Fragmentation patterns of plasma cell-free DNA (cfDNA) are known to reflect nucleosome positions of cell types contributing to cfDNA. Based on cfDNA fragmentation patterns, the deviation in nucleosome footprints was quantified between diagnosed ovarian cancer patients and healthy individuals. Multinomial modeling was subsequently applied to capture these deviations in a per sample nucleosome footprint score. Validation was performed in 271 cfDNAs pre-surgically collected from women with an adnexal mass. We confirmed that nucleosome scores were elevated in invasive carcinoma patients, but not in patients with benign or borderline disease. Combining nucleosome scores with chromosomal instability scores assessed in the same cfDNA improved prediction of malignancy. Nucleosome scores were, however, more reliable to predict non-high-grade serous ovarian tumors, which are characterized by low chromosomal instability. These data highlight that compared to chromosomal instability, nucleosome footprinting provides a complementary and more generic read-out for pre-surgical diagnosis of invasive disease in women with adnexal masses.

Familial risk of epithelial ovarian cancer after accounting for gynaecological surgery: a population-based study. ME Barnard, H Meeks, EA Jarboe, J Albro, NJ Camp, r A Doherty. Journal of Medical Genetics 2022. doi: 10.1136/jmedgenet-2021-108402 https://jmg.bmj.com/content/early/2022/05/08/jmedgenet-2021-108402.abstract

Background Uptake of risk-reducing surgery has increased among women at high risk of epithelial ovarian cancer. We sought to characterise familial risk of epithelial ovarian cancer histotypes in a population-based study after accounting for gynaecological surgeries, including bilateral oophorectomy.

Methods We compared risk of epithelial ovarian cancer in relatives of 3536 epithelial ovarian cancer cases diagnosed in 1966–2016 and relatives of 35 326 matched controls. We used Cox competing risk models, incorporating bilateral oophorectomy as a competing risk, to estimate the relative risk of ovarian cancer in first-degree (FDR), second-degree (SDR) and third-degree (TDR) relatives from 1966 to 2016. We also estimated relative risks in time periods before (1966–1994, 1995–2004) and after (2005–2016) formal recommendations were made for prophylactic oophorectomy among women with pathogenic variants in BRCA1/2.

Results The relative risks of epithelial ovarian cancer in FDRs, SDRs and TDRs of cases versus controls were 1.68 (95% CI 1.39 to 2.04), 1.51 (95% CI 1.30 to 1.75) and 1.34 (95% CI 1.20 to 1.48), respectively. Relative risks were greatest for high-grade serous, mucinous and 'other epithelial' histotypes. Relative risks were attenuated for case FDRs, but not for SDRs or TDRs, from 2005 onwards, consistent with the timing of recommendations for prophylactic surgery.

Conclusion Familial risk of epithelial ovarian cancer extends to TDRs, especially for high-grade serous and mucinous histotypes. Distant relatives share genes but minimal environment, highlighting the importance of germline inherited genetics in ovarian cancer aetiology. Increased ovarian cancer risk in distant relatives has implications for counselling and recommendations for prophylactic surgeries that, from our data, appear only to reach FDRs.

Racial and Ethnic Differences in Hysterectomy-Corrected Uterine Corpus Cancer Mortality by Stage and Histologic Subtype. MA Clarke, SS Devesa, A Hammer, N Wentzensen. JAMA Oncol. Published online May 05, 2022. doi:10.1001/jamaoncol.2022.0009 https://jamanetwork.com/journals/jamaoncology/article-abstract/2792010

Key Points

Question Do uterine cancer mortality trends vary by tumor characteristics according to race and ethnicity?

Findings In this cohort study of 208 587 women with uterine cancer, linked mortality and cancer registry data showed uterine cancer mortality rate annual increases of 3.4% among Asian women, 3.5% among Black women, 6.7% among Hispanic women, and 1.5% among White women, irrespective of histologic subtype or stage at diagnosis. Mortality rates were found to have increased by 1.8% for uterine cancer overall and 2.7% for nonendometrioid subtypes, whereas mortality rates of less-aggressive endometrioid cancers remained stable.

Meaning These findings suggest that increasing uterine cancer mortality is associated with increasing rates of aggressive nonendometrioid carcinomas, but racial and ethnic disparities cannot solely be explained by histologic subtype and stage at diagnosis.

Abstract

Importance Uterine cancer incidence has been increasing, particularly rates of aggressive, nonendometrioid subtypes, which are disproportionately higher among non-Hispanic Black women. The association of subtype-specific trends with uterine cancer mortality and with the role of tumor subtype and stage at diagnosis with racial disparities in uterine cancer deaths at the population-based level are not known.

Objective To estimate histologic subtype- and stage-specific uterine cancer mortality rates by race and ethnicity, corrected for hysterectomy.

Design, Setting, and Participants This cohort study used the US Surveillance, Epidemiology, and End Results–18 Incidence-Based Mortality database, representing approximately 26% of the US population and including deaths that occurred from 2000 to 2017. Hysterectomy correction was based on hysterectomy prevalence data from the Behavioral Risk Factor Surveillance System. Uncorrected and corrected rates associated with uterine corpus cancer cases diagnosed between 2000 and 2017 and uterine corpus cancer deaths occurring between 2010 and 2017 were age-adjusted to the 2000 US standard population and are expressed per 100 000 person-years, and annual percent changes in rates were calculated using log-linear regression. Data analysis was performed from March 10 to May 20, 2021.

Exposures Tumor histologic subtype, cancer stage at diagnosis, and race and ethnicity**.**

Results Among 208 587 women diagnosed with uterine cancer during 2000-2017 (15 983 [7.7%] were Asian; 20 302 [9.7%] Black; 23 096 [11.1%] Hispanic; and 149 206 [71.5%] White individuals), there were 16 797 uterine cancer deaths between 2010 and 2017, corresponding to a hysterectomy-corrected mortality rate of 15.7 per 100 000 person-years. Hysterectomy-corrected rates were highest among Black women, overall, by histologic subtype and stage at diagnosis. Among all women, uterine corpus cancer mortality rates increased significantly by 1.8% (95% CI, 1.5%-2.9%) per year from 2010 to 2017, as did rates of nonendometrioid carcinomas (2.7%; 95% CI, 1.8%-3.6%), with increases occurring in Asian (3.4%; 95% CI, 0.3%-6.6%), Black (3.5%; 95% CI, 2.2%-4.9%), Hispanic (6.7%; 95% CI, 1.9%-11.8%), and White women (1.5%; 95% CI, 0.6%-2.4%). In contrast, endometrioid carcinoma mortality rates remained stable.

Conclusions and Relevance The findings of this cohort study suggest a significant increase of nonendometrioid uterine carcinoma mortality rates, aligning with recent incidence trends. The factors associated with these trends are not well understood and require more investigation of possible mechanisms. Despite stable incidence rates, endometrioid cancer mortality rates have not decreased over the past decade at the population level, suggesting limited progress in treatment for these cancers. The substantial disparities in uterine corpus cancer mortality rates among non-Hispanic Black women cannot be fully explained by subtype distribution and stage at diagnosis.

Comparison of Cancer-Related Spending and Mortality Rates in the US vs 21 High-Income Countries. RD Chow, EH Bradley, CP Gross. JAMA Health Forum. 2022;3(5):e221229. doi:10.1001/jamahealthforum.2022.1229 https://jamanetwork.com/journals/jama-health-forum/fullarticle/2792761

Key Points

Question Is spending on cancer care associated with lower cancer mortality rates?

Findings In this cross-sectional study of 22 high-income countries, national cancer care expenditures in 2020 were not associated with age-standardized cancer mortality rates. Although the US had the highest per capita spending on cancer

care, after adjustment for smoking, the US cancer mortality rate was comparable with that of the median high-income country.

Meaning Results of this cross-sectional study suggest that understanding how countries outside the US achieve lower cancer mortality rates with lower spending may prove useful to future researchers, clinicians, and policy makers seeking to best serve their populations.

Abstract

Importance Studies using data from before 2011 concluded that the cost of US cancer care is justified given improved outcomes compared with European countries. However, it is unclear whether contemporary US cancer care provides better value than that of other high-income countries.

Objective To assess whether cancer mortality rates in 2020 were lower in countries with higher cancer-related spending, and to estimate across countries the incremental cost per averted cancer death.

Design, Setting, and Participants Cross-sectional, national-level analysis of 22 high-income countries, assessing the association between cancer care expenditures and age-standardized population-level cancer mortality rates in 2020, with and without adjustment for smoking. In addition, US incremental costs per averted death compared with the other countries were calculated. This study was conducted from September 1, 2021, to March 31, 2022.

Main Outcomes and Measures Age-standardized population-level cancer mortality rates.

Results In this cross-sectional study of 22 countries, the median cancer mortality rate was 91.4 per 100 000 population (IQR, 84.2-101.6). The US cancer mortality rate was higher than that of 6 other countries (86.3 per 100 000). Median per capita spending in USD for cancer care was $296 (IQR, $222-$348), with the US spending more than any other country ($584). After adjusting for smoking, 9 countries had lower cancer care expenditures and lower mortality rates than the US. Of the remaining 12 countries, the US additionally spent more than $5 million per averted death relative to 4 countries, and between $1 and $5 million per averted death relative to 8 countries. Cancer care expenditures were not associated with cancer mortality rates, with or without adjustment for smoking (Pearson R = −0.05 [95% CI, −0.46 to 0.38]; P = .81; and R = −0.05 [95% CI, −0.46 to 0.38]; P = .82).

Conclusions and Relevance In this cross-sectional study of national cancer care expenditures and cancer mortality rates across 22 countries, although the cancer mortality rate in the US was lower than the median, the US spent twice as much on cancer care as the median country. Findings of this study suggest that the US expenditure on cancer care may not be commensurate with improved cancer outcomes.

Test Performance of Cervical Cytology Among Adults With vs Without Human Papillomavirus Vaccination. D Teoh, G Nam, DA Aase, R Russell, GB Melton, S Kulasingam, RI Vogel. JAMA Netw Open. 2022;5(5):e2214020. doi:10.1001/jamanetworkopen.2022.14020
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2792673?guestAccessKey=2b737768-9ca1-4e72-91fa-bc3546b02a1a&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question Is the positive predictive value of abnormal cervical cytology lower among individuals who have been vaccinated against human papillomavirus?

Findings In a cohort study of 46 988 patients aged 21 to 35 years participating in cervical cancer screening, the positive predictive value of cervical cytology for cervical intraepithelial neoplasia 2 and more severe diagnoses was significantly lower among vaccinated individuals (17.4%) than unvaccinated individuals (21.3%).

Meaning The observed increased risk of a false-positive cervical cytology result for individuals vaccinated against HPV may warrant screening guidelines that stratify by vaccination status to minimize the risks of overscreening and overtreatment among individuals with low risk for cervical cancer.

Abstract

Importance Current US cervical cancer screening guidelines do not differ by human papillomavirus (HPV) vaccination status. However, as the positive predictive value (PPV) of a screening test decreases, the risk of a false-positive result increases.

Objective To evaluate whether HPV vaccination is associated with decreased PPV for abnormal cervical cytology.

Design, Setting, and Participants This retrospective cohort study conducted via electronic medical record review included eligible patients aged 21 to 35 years who had at least 1 cervical cytology result within a single health system between January 2015 and December 2018. The health system comprises a partnership between an academic health center and a private not-for-profit health center. Patients with abnormal screening cytology and no diagnostic test results were omitted from analysis. Data were analyzed from December 2019 to November 2021.

Exposures HPV vaccination, defined as receiving at least 1 dose of HPV vaccine. Subgroup analyses were performed for those completing all vaccination doses per Advisory Committee on Immunization Practices guidelines and by age at vaccination initiation, dichotomized as younger than 21 years vs 21 years or older.

Main Outcomes and Measures PPV of abnormal cervical cytology for risk of cervical intraepithelial neoplasia (CIN) 2 or more severe diagnosis.

Results A total of 46 988 patients (mean [SD] age, 28.7 [4.5] years; 3058 [6.5%] Asian; 4159 [8.9%] Black or African American; 35 446 [75.4%] White) were included; 15 494 (33.0%) were at least partially vaccinated, and 4289 (9.1%) had abnormal cytology results during the study period. Among the individuals with abnormal cytology, the PPV for CIN 2 or more severe diagnosis was lower among vaccinated individuals (17.4%; 95% CI, 16.4%-18.4%) than unvaccinated individuals (21.3%; 95% CI, 20.4%-22.3%). Among vaccinated individuals, PPV was significantly lower among those completing vaccination (15.9%; 95% CI, 14.9%-17.0%) than those with incomplete vaccination (22.4%; 95% CI, 20.0%-25.0%), especially among those initiating vaccination when younger than 21 years (11.9%; 95% CI, 10.9%-12.9%) vs those initiating at age 21 years or older (30.7%; 95% CI, 27.3%-34.4%).

Conclusions and Relevance Among a population with relatively low HPV vaccine coverage, the PPV of cervical cytology for CIN 2 or more severe diagnosis was significantly lower among vaccinated individuals. PPV will likely further decrease in the future as a population with higher HPV vaccination coverage ages into screening. Confirmation of these results will call for changes in screening strategies, particularly for completely vaccinated individuals who initiated vaccination when younger than 21 years.

Development and Validation of an Explainable Machine Learning Model for Major Complications After Cytoreductive Surgery. H Deng, Z Eftekhari, C Carlin, J Veerapong, KF Fournier, FM Johnston, SP Dineen, BD Powers, Ryan Hendrix, LA Lambert, DE Abbott, K Vande Walle, TE Grotz, SH Patel, CN Clarke, CA Staley, S Abdel-Misih, JM Cloyd, B Lee, Y Fong, M Raoof. JAMA Netw Open. 2022;5(5):e2212930. doi:10.1001/jamanetworkopen.2022.12930

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2792675?guestAccessKey=d4f6ba33-4764-4284-be6b-db6a60be6aeb&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question Can machine learning provide superior risk prediction compared with the current statistical methods for patients undergoing cytoreductive surgery?

Findings In this prognostic study, an optimized machine learning model demonstrated superior capability of predicting individual-level risk of major complications after cytoreductive surgery than traditional methods. Cohort-level risk prediction allowed unbiased categorization of patients into 6 distinct surgical risk groups.

Meaning These results suggest that explainable machine learning methods cannot only provide accurate risk prediction but can also allow identification of potentially modifiable sources of risk on patient and cohort levels.

Abstract

Importance Cytoreductive surgery (CRS) is one of the most complex operations in surgical oncology with significant morbidity, and improved risk prediction tools are critically needed. Machine learning models can potentially overcome the limitations of traditional multiple logistic regression (MLR) models and provide accurate risk estimates.

Objective To develop and validate an explainable machine learning model for predicting major postoperative complications in patients undergoing CRS.

Design, Setting, and Participants This prognostic study used patient data from tertiary care hospitals with expertise in CRS included in the US Hyperthermic Intraperitoneal Chemotherapy Collaborative Database between 1998 and 2018. Information from 147 variables was extracted to predict the risk of a major complication. An ensemble-based machine learning (gradient-boosting) model was optimized on 80% of the sample with subsequent validation on a 20% holdout data set. The machine learning model was compared with traditional MLR models. The artificial intelligence SHAP (Shapley additive explanations) method was used for interpretation of patient- and cohort-level risk estimates and interactions to define novel surgical risk phenotypes. Data were analyzed between November 2019 and August 2021.

Exposures Cytoreductive surgery.

Main Outcomes and Measures Area under the receiver operating characteristics (AUROC); area under the precision recall curve (AUPRC).

Results Data from a total 2372 patients were included in model development (mean age, 55 years [range, 11-95 years]; 1366 [57.6%] women). The optimized machine learning model achieved high discrimination (AUROC: mean cross-validation, 0.75 [range, 0.73-0.81]; test, 0.74) and precision (AUPRC: mean cross-validation, 0.50 [range, 0.46-0.58]; test, 0.42). Compared with the optimized machine learning model, the published MLR model performed worse (test AUROC and AUPRC: 0.54 and 0.18, respectively). Higher volume of estimated blood loss, having pelvic peritonectomy, and longer operative time were the top 3 contributors to the high likelihood of major complications. SHAP dependence plots demonstrated insightful nonlinear interactive associations between predictors and major complications. For instance, high estimated blood loss (ie, above 500 mL) was only detrimental when operative time exceeded 9 hours. Unsupervised clustering of patients based on similarity of sources of risk allowed identification of 6 distinct surgical risk phenotypes.

Conclusions and Relevance In this prognostic study using data from patients undergoing CRS, an optimized machine learning model demonstrated a superior ability to predict individual- and cohort-level risk of major complications vs traditional methods. Using the SHAP method, 6 distinct surgical phenotypes were identified based on sources of risk of major complications.

A vaccine targeting resistant tumours by dual T cell plus NK cell attack. S Badrinath, MO Dellacherie, A Li, S Zheng, X Zhang, M Sobral, JW Pyrdol, KL Smith, Y Lu, S Haag, H Ijaz, F Connor-Stroud, T Kaisho, G Dranoff, G-C Yuan, DJ Mooney, KW Wucherpfennig. Nature (2022). https://doi.org/10.1038/s41586-022-04772-4

Most cancer vaccines target peptide antigens, necessitating personalization owing to the vast inter-individual diversity in major histocompatibility complex (MHC) molecules that present peptides to T cells. Furthermore, tumours frequently escape T cell-mediated immunity through mechanisms that interfere with peptide presentation. Here we report a cancer vaccine that induces a coordinated attack by diverse T cell and natural killer (NK) cell populations. The vaccine targets the MICA and MICB (MICA/B) stress proteins expressed by many human cancers as a result of DNA damage. MICA/B serve as ligands for the activating NKG2D receptor on T cells and NK cells, but tumours evade immune recognition by proteolytic MICA/B cleavage. Vaccine-induced antibodies increase the density of MICA/B proteins on the surface of tumour cells by inhibiting proteolytic shedding, enhance presentation of tumour antigens by dendritic cells to T cells and augment the cytotoxic function of NK cells. Notably, this vaccine maintains efficacy against MHC class I-deficient tumours resistant to cytotoxic T cells through the coordinated action of NK cells and CD4+ T cells. The vaccine is also efficacious in a clinically important setting: immunization following surgical removal of primary, highly metastatic tumours inhibits the later outgrowth of metastases. This vaccine design enables protective immunity even against tumours with common escape mutations.

HPV and DNA Methylation Testing in Urine for Cervical Intraepithelial Neoplasia and Cervical Cancer Detection. R van den Helder, RDM Steenbergen, AP van Splunter, CH Mom, MY Tjiong, I Martin, FMF Rosier-van Dunné, IM van der Avoort, MCG Bleeker, NE van Trommel. Clin Cancer Res 15 May 2022; 28 (10): 2061–2068. https://doi.org/10.1158/1078-0432.CCR-21-3710

Purpose: Biomarker detection in urine offers a potential solution to increase effectiveness of cervical cancer screening programs by attracting nonresponders. In this prospective study, the presence of high-risk human papillomavirus (hrHPV) DNA and the performance of DNA methylation analysis was determined for the detection of cervical cancer and high-grade cervical intraepithelial neoplasia (CIN2/3) in urine, and compared with paired cervicovaginal self-samples and clinician-taken cervical scrapes.

Experimental Design: A total of 587 samples were included from 113 women with cervical cancer, 92 women with CIN2/3, and 64 controls. Samples were tested for hrHPV DNA and five methylation markers. Univariate and multivariate logistic regression and leave-one-out cross-validation were used to determine the methylation marker performance for CIN3 and cervical cancer (CIN3+) detection in urine. Agreement between samples was determined using Cohen kappa statistics and the Spearman correlation coefficients.

Results: HrHPV presence was high in all sample types, 79% to 92%. Methylation levels of all markers in urine significantly increased with increasing severity of disease. The optimal marker panel (*ASCL1/LHX8*) resulted in an AUC of 0.84 for CIN3+ detection in urine, corresponding to an 86% sensitivity at a 70% predefined specificity. At this threshold 96% (109/113) of cervical cancers, 68% (46/64) of CIN3, and 58% (14/24) of CIN2 were detected. Between paired samples, a strong agreement for HPV16/18 genotyping and a fair to strong correlation for methylation was found.

Conclusions: HrHPV DNA and DNA methylation testing in urine offers a promising solution to detect cervical cancer and CIN2/3 lesions, especially for women currently unreached by conventional screening methods.

Comparative performance of the human papillomavirus test and cytology for primary screening for high-grade cervical intraepithelial neoplasia at the population level. E Hurtado-Salgado, Cárdenas-Cárdenas,J Salmerón,R Luna-Gordillo,E Ortiz-Panozo,B Allen-Leigh,N Saavedra-Lara,EL Franco,E Lazcano-Ponce. Int. J. Cancer. 2022; 150(9): 1422- 1430. doi:10.1002/ijc.33905

The World Health Organization recommends high-risk human papillomavirus (hrHPV)-based screening for women 39 to 49 years, based on the greater accuracy of hrHPV-based screening for cervical cancer detection. Many cervical cancer screening programs have incorporated hrHPV testing and multiple early cervical cancer detection strategies have been evaluated, mostly under controlled conditions. However, there are few evaluations of combined hrHPV and cytology strategies post-implementation at the population level. Our study sought to estimate the relative yield of hrHPV testing compared to cervical cytology, as a primary screening test for cervical intraepithelial neoplasia grade 2+ (CIN2+), used at the population level. We analyzed screening data from Mexico's public cervical cancer prevention program from 2010 to 2015 in women 35 to 64 years. The study population consisted of two cohorts: one from a total of 2 881 962 cytology-based screening tests and another from a total of 2 004 497 hrHPV-based screening tests, which are concurrent in time. We performed a relative yield analysis using Poisson regression models to compare the effectiveness of hrHPV testing for CIN2+ with cervical cytology. A total of 4 886 459 records were analyzed, including 23 999 biopsies; 0.12% (n = 6166) had a CIN2+ histologic diagnosis. hrHPV testing with cytological triage detects twice as many CIN2+ cases as screening using cytology alone.

What's new?

Many cervical cancer screening programmes have incorporated high-risk human papillomavirus (hrHPV) testing. However, there are few evaluations of combined hrHPV and cytology strategies at the population level. Using data from 4,886,459

screening tests and biopsies from 23,999 women 35–64 years of age over a 6-year period, this study compared the performance of hrHPV screening with cytological triage to cytology alone for early detection of high-grade cervical lesions. hrHPV screening with cytological triage detected twice as many CIN2+ cases as screening with cytology alone in the real-life conditions of a cervical cancer screening programme in a large middle-income country.

Acceleration of cervical cancer diagnosis with human papillomavirus testing below age 30: Observational study.

M Rebolj,CS Mathews,F Pesola,A Castañon,H Kitchener. Int. J. Cancer. 2022; 150(9): 1412-1421. doi:10.1002/ijc.33900 Int. J. Cancer. 2022; 150(9): 1412- 1421. doi:10.1002/ijc.33900

Several international cervical screening guidelines advise against using high-risk human papillomavirus (HR-HPV) testing in women younger than 30. The rationale for this in young women, lies in the potential for additional detection of both low-grade and high-grade cervical intraepithelial neoplasia (CIN) leading to unnecessary treatments without reducing the burden of cervical cancer. We studied 56 544 women screened at 24 to 29 with HR-HPV testing and 116 858 screened with liquid-based cytology (LBC) in the English HPV screening pilot. They were compared to 528 460 women screened at the age of 30 to 49. We studied the detection of cervical cancer and CIN2/3 across two consecutive screening rounds 3 years apart. At 24 to 29, a positive HR-HPV test detected more cases of cervical cancer in the prevalence round than did a positive LBC test (1.36/1000 screened vs 0.82/1000, ORadj: 1.61, 95% CI: 1.18-2.19). In women with a negative HR-HPV test, cervical cancer was diagnosed before or at the incidence round in 0.07/1000. After a negative LBC test, cancer detection reached 0.47/1000 and 40% of these cases were diagnosed at FIGO stage IB+. HR-HPV testing increased the detection of CIN2/3 diagnoses in two consecutive rounds combined by 30% (71.9/1000 vs 55.2/1000). The patterns of detection of cervical cancer and CIN2/3 were almost identical at older ages. These data support using HR-HPV testing for screening of women younger than 30, which not only accelerates the diagnosis of cervical cancer but leads to a similar relative increase in CIN2/3 diagnosis to that found in women aged 30 to 49.

Prospective evaluation of 92 serum protein biomarkers for early detection of ovarian cancer

T Mukama, RT Fortner, V Katzke, LC Hynes, A Petrera, SM Hauck, T Johnson, M Schulze, C Schiborn, AL Rostgaard-Hansen, A Tjønneland, K Overvad, MJS Pérez, M Crous-Bou, M-D Chirlaque, P Amiano, E Ardanaz, EL Watts, RC Travis, C Sacerdote, S Grioni, G Masala, Sa Signoriello, R Tumino, IT Gram, TM Sandanger, H Sartor, E Lundin, A Idahl, AK Heath, L Dossus, E Weiderpass, R Kaaks.

Background CA125 is the best available yet insufficiently sensitive biomarker for early detection of ovarian cancer. There is a need to identify novel biomarkers, which individually or in combination with CA125 can achieve adequate sensitivity and specificity for the detection of earlier-stage ovarian cancer.

Methods In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, we measured serum levels of 92 preselected proteins for 91 women who had blood sampled ≤18 months prior to ovarian cancer diagnosis, and 182 matched controls. We evaluated the discriminatory performance of the proteins as potential early diagnostic biomarkers of ovarian cancer.

Results Nine of the 92 markers; CA125, HE4, FOLR1, KLK11, WISP1, MDK, CXCL13, MSLN and ADAM8 showed an area under the ROC curve (AUC) of ≥0.70 for discriminating between women diagnosed with ovarian cancer and women who remained cancer-free. All, except ADAM8, had shown at least equal discrimination in previous case-control comparisons. The discrimination of the biomarkers, however, was low for the lag-time of >9–18 months and paired combinations of CA125 with any of the 8 markers did not improve discrimination compared to CA125 alone.

Conclusion Using pre-diagnostic serum samples, this study identified markers with good discrimination for the lag-time of 0–9 months. However, the discrimination was low in blood samples collected more than 9 months prior to diagnosis, and none of the markers showed major improvement in discrimination when added to CA125.

Integrative genomic and transcriptomic analysis reveals immune subtypes and prognostic markers in ovarian clear cell carcinoma

S Ye, Q Li, Y Wu, W Jiang, S Zhou, X Zhou, W Yang, X Tu, B Shan, S Huang, H Yang. Br J Cancer. 2022 May;126(8):1215-1223. doi: 10.1038/s41416-022-01705-w. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9023449/

Background We performed an integrative genomic and transcriptomic profiling to identify molecular subtypes and prognostic markers with special focus on immune-related pathways.

Methods Totally, 50 Chinese patients were subjected to targeted next-generation sequencing and transcriptomic sequencing.

Results Two distinct subgroups were identified as immune (22.0%) and non-immune (78.0%) based on the immune-pathway related hierarchical clustering. Surprisingly, patients with immune subtype had a significantly worse survival. The prognostic capacity was validated in external cohorts. The immune group had higher expression of genes involved in pro-inflammation and checkpoints. PD-1 signalling pathway was enriched in the immune subtype. Besides, the immune cluster presented enriched expression of genes involved in epithelial-mesenchymal transition, angiogenesis and PI3K-AKT-mTOR signalling, while the non-immune subtype had higher expression of metabolic pathways. The immune subtype had a higher mutation rate of PIK3CA though significance was not achieved. Lastly, we established a prognostic immune signature for

overall survival. Interestingly, the immune signature could also be applied to renal clear cell carcinoma, but not to other histologic subtype of ovarian cancer.
Conclusions An immune subtype of OCCC was identified with poor survival and enrichment of PD-1 and PI3K-AKT-mTOR signalling. We constructed and validated a robust prognostic immune signature of OCCC patients.

Secondary Cytoreductive Surgery in Platinum-Sensitive Recurrent Ovarian Cancer: A Meta-Analysis. MH Baek, EY Park, HI Ha, SY Park, MC Lim, C Fotopoulou, RE Bristow. J Clin Oncol. 2022 May 20;40(15):1659-1670. doi: 10.1200/JCO.21.02085. https://pubmed.ncbi.nlm.nih.gov/35188810/#affiliation-8
Purpose: The survival impact of secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer was studied.
Methods: We identified published studies from 1983 to 2021 following our inclusion criteria from MEDLINE, EMBASE, and Cochrane library. To integrate the effect size of single-arm studies, meta-analysis was performed using death rate as a primary outcome. The effect of complete cytoreduction and optimal cytoreduction on survival was evaluated using meta-regression. The pooled death rate was presented with a 95% CI. The publication bias was evaluated with the funnel plot and Egger's test, and sensitivity analysis was performed. To overcome missing death rates, the linear regression model was performed on log-transformed median overall survival (OS) time using study size as a weight.
Results: Thirty-six studies with 2,805 patients reporting death rates were used for this meta-analysis of the 80 eligible studies. There was strong heterogeneity, with the *P* value of the Cochrane Q test of < 0.0001 and Higgins's I^2 statistics of 86%; thus, we considered a random effect model. The pooled death rate was 44.2% (95% CI, 39.0 to 49.5), and both the complete and optimal cytoreductions were associated with better survival outcomes as significant moderators in the meta-regression model (*P* < .001 and *P* = .005, respectively). Although 14 studies were located outside the funnel plot, Egger's test indicated no publication bias (*P* = .327). A sensitivity analysis excluding 14 studies showed similar results. In the linear regression model on the basis of 57 studies, the median OS time increased by 8.97% and 7.04% when the complete and optimal cytoreduction proportion increased by 10%, respectively, after adjusting other variables.
Conclusion: Secondary cytoreductive surgery, resulting in maximal tumor resection, significantly prolongs OS in platinum-sensitive recurrent ovarian cancer.

Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants
S Li, V Silvestri, G Leslie, TR Rebbeck, SL Neuhausen, JL Hopper, H Roed Nielsen, A Lee, X Yang, L McGuffog, MT Parsons, IL Andrulis, N Arnold, M Belotti, Å Borg, B Buecher, SS. Buys, S M Caputo, WK Chung, C Colas, SV Colonna, J Cook, MB Daly, M de la Hoya, A de Pauw, H Delhomelle, J Eason, C Engel, DG Evans, U Faust, TN Fehm, F Fostira, G Fountzilas, M Frone, V Garcia-Barberan, P Garre, M Gauthier-Villars, A Gehrig, G Glendon, DE Goldgar, L Golmard, MH Greene, E Hahnen, U Hamann, H Hanson, T Hassan, J Hentschel, J Horvath, L Izatt, R Janavicius, Y Jiao, EM John, BY Karlan, S-W Kim, I Konstantopoulou, A Kwong, A Laugé, JW Lee, F Lesueur, N Mebirouk, A Meindl, E Mouret-Fourme, H Musgrave, JNY Yie, D Niederacher, SK Park, IS Pedersen, J Ramser, SJ Ramus, J Rantala, MU Rashid, F Reichl, J Ritter, A Rump, M Santamariña, C Saule, G Schmidt, RK Schmutzler, L Senter, S Shariff, CF Singer, MC Southey, D Stoppa-Lyonnet, C Sutter, Y Tan, SH Teo, MB Terry, M Thomassen, M Tischkowitz, AE Toland, D Torres, A Vega, SA Wagner, S Wang-Gohrke, B Wappenschmidt, BHF Weber, D Yannoukakos, AB Spurdle, DF Easton, G Chenevix-Trench, L Ottini, AC Antoniou. Journal of Clinical Oncology 2022 40:14, 1529-1541 DOI: 10.1200/JCO.21.02112 https://ascopubs.org/doi/full/10.1200/JCO.21.02112
PURPOSE To provide precise age-specific risk estimates of cancers other than female breast and ovarian cancers associated with pathogenic variants (PVs) in *BRCA1* and *BRCA2* for effective cancer risk management.
METHODS We used data from 3,184 *BRCA1* and 2,157 *BRCA2* families in the Consortium of Investigators of Modifiers of *BRCA1/2* to estimate age-specific relative (RR) and absolute risks for 22 first primary cancer types adjusting for family ascertainment.
RESULTS *BRCA1* PVs were associated with risks of male breast (RR = 4.30; 95% CI, 1.09 to 16.96), pancreatic (RR = 2.36; 95% CI, 1.51 to 3.68), and stomach (RR = 2.17; 95% CI, 1.25 to 3.77) cancers. Associations with colorectal and gallbladder cancers were also suggested. *BRCA2* PVs were associated with risks of male breast (RR = 44.0; 95% CI, 21.3 to 90.9), stomach (RR = 3.69; 95% CI, 2.40 to 5.67), pancreatic (RR = 3.34; 95% CI, 2.21 to 5.06), and prostate (RR = 2.22; 95% CI, 1.63 to 3.03) cancers. The stomach cancer RR was higher for females than males (6.89 *v* 2.76; *P* = .04). The absolute risks to age 80 years ranged from 0.4% for male breast cancer to approximately 2.5% for pancreatic cancer for *BRCA1* carriers and from approximately 2.5% for pancreatic cancer to 27% for prostate cancer for *BRCA2* carriers.
CONCLUSION In addition to female breast and ovarian cancers, *BRCA1* and *BRCA2* PVs are associated with increased risks of male breast, pancreatic, stomach, and prostate (only *BRCA2* PVs) cancers, but not with the risks of other previously suggested cancers. The estimated age-specific risks will refine cancer risk management in men and women with *BRCA1/2* PVs

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Human Papillomavirus Infection Determines Prognosis in Cervical Cancer. J Lei, LS Arroyo-Mühr, C Lagheden, C Eklund, SN Kleppe, M Elfström, B Andrae, P Sparén, J Dillner, K Sundström. Journal of Clinical Oncology 2022 40:14, 1522-1528 DOI: 10.1200/JCO.21.01930 https://ascopubs.org/doi/full/10.1200/JCO.21.01930

PURPOSE Detection of human papillomavirus (HPV) by polymerase chain reaction in invasive cervical cancer is strongly associated with prognosis but previous studies have not considered sequencing efforts. We aimed to assess the association when also including comprehensive analysis of HPV infection by deep sequencing and a longer follow-up period.

MATERIALS AND METHODS We subjected all 392 of 2,845 invasive cervical cancer cases that were polymerase chain reaction–negative for HPV to RNA sequencing on the NovaSeq 6000 platform (Illumina) and identified an additional 169 cases as HPV-positive. We followed all women from date of diagnosis to December 31, 2016, emigration, or death, whichever occurred first. The main outcome was all-cause mortality by December 31, 2016. We calculated 5-year cumulative relative survival ratios compared with the female general population and used Poisson regression to estimate excess hazard ratios of all-cause mortality by infection with any of the 13 most oncogenic (high-risk [hr]) HPV types in the tumor. All models were adjusted for age, time since diagnosis, stage, histology, and education level.

RESULTS The 5-year cumulative relative survival ratio was 0.45 (95% CI, 0.39 to 0.51) in the hrHPV-negative group, and 0.74 (95% CI, 0.72 to 0.75) in the hrHPV-positive group. This translated to a statistically significantly 43% lower excess mortality in the hrHPV-positive group compared with the hrHPV-negative (corresponding to an excess hazard ratio 0.57; 95% CI, 0.48 to 0.69). There was no association between HPV risk group, clade, or number of HPV infections and prognosis.

CONCLUSION hrHPV status is a strong determinant of cervical cancer prognosis over 15 years after diagnosis, above and beyond other established factors.

Topical imiquimod versus surgery for vulvar intraepithelial neoplasia: a multicentre, randomised, phase 3, non-inferiority trial. G Trutnovsky, O Reich, EA Joura, M Holter, A Ciresa-König, A Widschwendter, C Schauer, G Bogner, Z Jan, A Boandl, MS Kalteis, S Regauer, K Tamussino. The Lancet 399 (10337) 2022, 1790-1798, https://doi.org/10.1016/S0140-6736(22)00469-X. (https://www.sciencedirect.com/science/article/pii/S014067362200469X)

Background The optimal management of vulvar high-grade squamous intraepithelial lesions (vHSILs) is challenging. Surgery is the standard treatment, but recurrences are observed in half of patients. Medical treatment with imiquimod is an effective alternative, but the two modalities have not been compared in a randomised trial. The aim of this study was to compare the clinical effectiveness, histological response, human papillomavirus (HPV) clearance, acceptance, and psychosexual morbidity of primary imiquimod treatment versus surgical treatment in women with vHSIL.

Methods This study was a multicentre, randomised, phase 3, non-inferiority clinical trial done by the Austrian Gynaecological Oncology group at six hospitals in Austria. We recruited female patients aged 18–90 years with histologically confirmed vHSIL with visible unifocal or multifocal lesions. Main exclusion criteria were clinical suspicion of invasion, a history of vulvar cancer or severe inflammatory dermatosis of the vulva, and any active treatment for vHSIL within the previous 3 months. Women with known immunodeficiency, who were pregnant, or who were lactating were excluded. Patients were randomly assigned (1:1) by block randomisation to imiquimod or surgery, and stratified by unifocal or multifocal disease. Treatment with imiquimod was self-administered in a slowly escalating dosage scheme up to three times per week for a period of 4–6 months. Surgery consisted of excision or ablation. Patients were assessed with vulvoscopy, vulvar biopsy, HPV tests, and patient-reported outcomes at baseline and after 6 months and 12 months. The primary endpoint was complete clinical response (CCR) at 6 months after local imiquimod treatment or one surgical intervention. Primary analysis was per protocol with a non-inferiority margin of 20%. This trial is registered at ClinicalTrials.gov, NCT01861535.

Findings 110 patients with vHSIL (78% with unifocal vHSIL and 22% with multifocal vHSIL) were randomly assigned between June 7, 2013, and Jan 8, 2020. Clinical response to treatment could be assessed in 107 patients (54 in the imiquimod group and 53 in the surgery group), and 98 patients (46 in the imiquimod group and 52 in the surgery group) completed the study per protocol. 37 (80%) of 46 patients using imiquimod had CCR, compared with 41 (79%) of 52 patients after one surgical intervention, showing non-inferiority of the new treatment (difference in proportion –0·016, 95% CI –0·15 to –0·18; p=0·0056). Invasive disease was found in five patients at primary or secondary surgery, but not in patients with per-protocol imiquimod treatment. There was no significant difference in HPV clearance, adverse events, and treatment satisfaction between study groups.

Interpretation

Imiquimod is a safe, effective, and well accepted alternative to surgery for women with vHSIL and can be considered as first-line treatment.

Tables of contents for Gynecologic Oncology:

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[*] ***In The Know*** (aka *Ed's List*) is prepared for the education of our fellows & candidate fellows on a monthly basis. It's purpose and intent is to make those involved in training aware of significant contributions to the field of Gynecologic Oncology. Two successive months of literature are put together to accommodate on line vs print appearances and to compensate for delays in a publication (i.e. the March material is not available until June).