In The Know

Gyn Onc Literature of Significance

Ed's List
February 2022

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

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February

Significance of Pelvic Fluid Observed during Ovarian Cancer Screening with Transvaginal Sonogram. JW Gorski, CS Dietrich III, C Davis, L Erol, H Dietrich, NJ Per, EL Ferrell L, AB McDowell, MJ Riggs, ML Hutchcraft , LA Baldwin-Branch, RW Miller, CP DeSimone, HH Gallion, FR Ueland, JR van Nagell Jr., EJ Pavlik. Diagnostics. 2022; 12(1):144. https://doi.org/10.3390/diagnostics12010144 https://www.mdpi.com/2075-4418/12/1/144/htm

The primary objective was to examine the role of pelvic fluid observed during transvaginal ultrasonography (TVS) in identifying ovarian malignancy. A single-institution, observational study was conducted within the University of Kentucky Ovarian Cancer Screening trial from January 1987 to September 2019. We analyzed true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) groups for the presence of pelvic fluid during screening encounters. Measured outcomes were the presence and duration of fluid over successive screening encounters. Of the 48,925 women surveyed, 2001 (4.1%) had pelvic fluid present during a TVS exam. The odds ratio (OR) of detecting fluid in the comparison group (TN screen; OR = 1) significantly differed from that of the FP cases (benign pathology; OR: 13.4; 95% confidence interval (CI): 9.1–19.8), the TP cases with a low malignant potential (LMP; OR: 28; 95% CI: 26.5–29.5), TP ovarian cancer cases (OR: 50.4; 95% CI: 27.2–93.2), and FN ovarian cancer cases (OR: 59.3; 95% CI: 19.7–178.1). The mean duration that pelvic fluid was present for women with TN screens was 2.2 ± 0.05 encounters, lasting 38.7 ± 1.3 months. In an asymptomatic screening population, free fluid identified in TVS exams was more associated with ovarian malignancy than in the control group or benign ovarian tumors. While pelvic free fluid may not solely discriminate malignancy from non-malignancy, it appears to be clinically relevant and warrants thoughtful consideration.

The WID-BC-index identifies women with primary poor prognostic breast cancer based on DNA methylation in cervical samples. JE. Barrett, C Herzog, A Jones, OC Leavy, I Evans, S Knapp, D Reisel, T Nazarenko, Y-NKim, D Franchi, A Ryan, J Franks, L Bjørge, M Zikan, D Cibula, N Harbeck, N Colombo, F Dudbridge, L Jones, K Sundström, J Dillner, AF Rådestad, K Gemzell-Danielsson, N Pashayan, M Widschwendter. Nat Commun 13, 449 (2022). https://doi.org/10.1038/s41467-021-27918-w

Genetic and non-genetic factors contribute to breast cancer development. An epigenome-based signature capturing these components in easily accessible samples could identify women at risk. Here, we analyse the DNA methylome in 2,818 cervical, 357 and 227 matched buccal and blood samples respectively, and 42 breast tissue samples from women with and without breast cancer. Utilising cervical liquid-based cytology samples, we develop the DNA methylation-based Women's risk IDentification for Breast Cancer index (WID-BC-index) that identifies women with breast cancer with an AUROC (Area Under the Receiver Operator Characteristic) of 0.84 (95% CI: 0.80–0.88) and 0.81 (95% CI: 0.76–0.86) in internal and external validation sets, respectively. CpGs at progesterone receptor binding sites hypomethylated in normal breast tissue of women with breast cancer or in BRCA mutation carriers are also hypomethylated in cervical samples of women with poor prognostic breast cancer. Our data indicate that a systemic epigenetic programming defect is highly prevalent in women who develop breast cancer. Further studies validating the WID-BC-index may enable clinical implementation for monitoring breast cancer risk.

These investigators suggest that by analyzing cervical cells' genomes, it may be possible to find genetic signatures that predict the risk of ovarian, breast, and endometrial cancers and flag patients that should be monitored more aggressively.

The Changing Landscape of Gynecologic Cancer Mortality in the United States. A N Giaquinto, R Broaddus, A Jemal, RL Siegel. Obstetrics & Gynecology: 2022 139 (3) 440-442 doi: 10.1097/AOG.0000000000004676 https://journals.lww.com/greenjournal/Fulltext/2022/03000/The_Changing_Landscape_of_Gynecologic_Cancer.12.aspx
Uterine corpus cancer mortality is now similar to that for ovarian cancer, and the disproportionate burden among Black women is widening.

The impact of olaparib dose reduction and treatment interruption on treatment outcome in the SOLO2/ENGOT-ov21 platinum-sensitive recurrent ovarian cancer. KE Francis, SI Kim, M Friedlander, V Gebski, I Ray Coquard, A Clamp, RT Penson, A Oza, T Perri, T. Huzarski, C. Martin-Lorente, S.C. Cecere, N. Colombo, B. Ataseven, K. Fujiwara, G. Sonke, I. Vergote, E Pujade-Lauraine, J-W Kim, CK Lee. Annals of Oncology 2022 https://doi.org/10.1016/j.annonc.2022.02.222. https://www.sciencedirect.com/science/article/pii/S0923753422003386

Background Maintenance treatment with poly (ADP-ribose) polymerase (PARP) inhibitor is now the standard of care in patients with *BRCA* mutated platinum-sensitive recurrent ovarian cancer following response to chemotherapy. In the SOLO2 trial, adverse event (AE) associated olaparib interruption, dose reduction, and discontinuation occurred in 50%, 28%, and 17% of patients, respectively. We used data from SOLO2 trial to evaluate the impact of dose alterations on survival outcomes and identified baseline characteristics associated with dose alteration.

Patients and methods We computed relative dose intensity (RDI) defined as received dose as a percentage of the standard dose (300mg twice a day) during the first twelve weeks on treatment. Patients were categorized into RDI >98%, RDI 90-98% and RDI < 90%. The association between RDI categories with progression-free survival (PFS) and overall survival (OS) were examined using a 12-week landmark Cox regression analysis. Logistic regression analysis was used to correlate baseline factors with RDI at 12-weeks.

Results In patients on olaparib included in the landmark analysis (n = 185) the mean 12-week RDI was 91.4%. There was no significant difference across 12-week RDI >98% (n = 110), 90-98% (n = 29), and <90% (n = 45) categories for PFS (median, 14.2 vs. 19.3 vs. 34.4 months; *P*=.37) and OS (median, 49.7 vs. 49.5 vs. 54.1 months; *P*=.84). Risk of RDI ≤90% increased with baseline performance status 1 (OR: 2.54; 95% CI: 1.11-5.82) any nausea (OR: 3.17; 95% CI: 0.9-11.23) and with body weight ≤ 70kg (OR: 1.86; 95% CI: 0.92-3.76).

Conclusions Dose reduction and interruption for the management of olaparib associated AE during the first 12 weeks did not impact on PFS and OS. When counselling patients requiring dose reductions or interruptions due to AEs, the results of this study will help assure patients that their outcomes will not be adversely affected.

Highlights:

- In the SOLO2 trial of olaparib (BRCA mutated PSROC), dose reductions and interruptions were used to manage AE
- These dose reductions and interruptions during the first 12 weeks of treatment did not impact on PFS and OS
- Relative dose intensity of ≤90% was most strongly associated with a baseline performance status of 1, compared to PS 0
- Results will help to assure patients that their outcomes will not be adversely affected by AE related dose alterations

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Subsequent Ultrasonographic Non-Visualization of the Ovaries Is Hastened in Women with Only One Ovary Visualized Initially. EJ Pavlik, H Fancher, CS Dietrich, JR van Nagell Jr. Healthcare. 2022; 10(3):433. https://doi.org/10.3390/healthcare10030433

Because the effects of age, menopausal status, weight and body mass index (BMI) on ovarian detectability by transvaginal ultrasound (TVS) have not been established, we determined their contributions to TVS visualization of the ovaries when one or both ovaries are visualized on the first ultrasound exam. A total of 29,877 women that had both ovaries visualized on their first exam were followed over 202,639 prospective TVS exams and 9703 women that had only one ovary visualized on their first exam were followed over 63,702 ultrasonography exams. All images were reviewed by a physician. While non-visualization of both ovaries increased with age in women selected on the basis of the visualization of only one ovary on their first ultrasound exam, one or both ovaries could be visualized in two out of every three women at 80 years of age and more than 50% of women over 80 years of age. At each age, more non-visualizations were associated with women that had only one ovary visualized on their first visit. Having only one ovary visualized on the first exam advanced non-visualizations by an average of ~10 years across all ages and by >20 years in women under 40 years of age. Conclusions: Having only one ovary visualized on an initial ultrasound exam considerably hastens complete non-visualization for this population; however, in these women, ovaries can still be visualized well past menopause, and body habitus is not limiting to TVS ovarian imaging, thus TVS should be considered capable of capturing an ovarian image in two out of every three women at 80 years of age.

Racial differences in the tumor immune landscape and survival of women with high-grade serous ovarian carcinoma. LC Peres, C Colin-Leitzinger, S Sinha, JR Marks, JR Conejo-Garcia, AJ Alberg, EV Bandera, A Berchuck, ML Bondy, BC Christensen, ML Cote, JA Doherty, PG Moorman, ES Peters, CM Segura, JV Nguyen, AG Schwartz, PD Terry, CM Wilson, BL Fridley, JM Schildkraut. Cancer Epidemiol Biomarkers Prev cebp.1334.2021.

https://aacrjournals.org/cebp/article/doi/10.1158/1055-9965.EPI-21-1334/681824/Racial-differences-in-the-tumor-immune-landscape

Background. Tumor infiltrating lymphocytes (TILs) confer a survival benefit among ovarian cancer patients; however, little work has been conducted in racially diverse cohorts.

Methods. The present study investigated racial differences in the tumor immune landscape and survival of age- and stage-matched Non-Hispanic Black and Non-Hispanic White women with high-grade serous ovarian carcinoma (HGSOC) enrolled in two population-based studies (n=121 in each racial group). We measured TILs (CD3+), cytotoxic T-cells (CD3+CD8+), regulatory T-cells (CD3+FoxP3+), myeloid cells (CD11b+), and neutrophils (CD11b+CD15+) via multiplex immunofluorescence. Multivariable Cox proportional hazard regression was used to estimate the association between immune cell abundance and survival overall and by race.

Results. Overall, higher levels of TILs, cytotoxic T-cells, myeloid cells, and neutrophils were associated with better survival in the intratumoral and peritumoral region, irrespective of tissue compartment (tumor, stroma). Improved survival was noted for T-regulatory cells in the peritumoral region and in the stroma of the intratumoral region, but no association for intratumoral T-regulatory cells. Despite similar abundance of immune cells across racial groups, associations with survival among Non-Hispanic White women were consistent with the overall findings, but among Non-Hispanic Black women, most associations were attenuated and not statistically significant.

Conclusions. Our results add to the existing evidence that a robust immune infiltrate confers a survival advantage among women with HGSOC; however, Non-Hispanic Black women may not experience the same survival benefit as Non-Hispanic White women with HGSOC. Impact. This study contributes to our understanding of the immunoepidemiology of HGSOC in diverse populations.

PTEN Loss and BRCA1 Promoter Hypermethylation Negatively Predict for Immunogenicity in BRCA-Deficient Ovarian Cancer. AA Kraya, KN Maxwell, MA Eiva, B Wubbenhorst, J Pluta, M Feldman, A Nayak, DJ Powell, SM Domchek, RH Vonderheide, KL Nathanson. JCO Precision Oncology 2022 :6 DOI: 10.1200/PO.21.00159

PURPOSE Ovarian cancers can exhibit a prominent immune infiltrate, but clinical trials have not demonstrated substantive response rates to immune checkpoint blockade monotherapy. We aimed to understand genomic features associated with immunogenicity in *BRCA1/2* mutation–associated cancers.

MATERIALS AND METHODS Using the Cancer Genome Atlas whole-exome sequencing, methylation, and expression data, we analyzed 66 ovarian cancers with either germline or somatic loss of *BRCA1/2* and whole-exome sequencing, immunohistochemistry, and CyTOF in 20 ovarian cancers with germline *BRCA1/2* pathogenic variants from Penn.

RESULTS We found two groups of *BRCA1/2* ovarian cancers differing in their immunogenicity: (1) 37 tumors significantly enriched for *PTEN* loss (11, 30%) and *BRCA1* promoter–hypermethylated (10, 27%; *P* = .0016) and (2) *PTEN* wild-type (28 of 29 tumors) cancers, with the latter group having longer overall survival (OS; *P* = .0186, median OS not reached *v* median OS = 66.1 months). *BRCA1/2*-mutant *PTEN* loss and *BRCA1* promoter–hypermethylated cancers were characterized by the decreased composition of lymphocytes estimated by gene expression (*P* = .0030), cytolytic index (*P* = .034), and cytokine expression but higher homologous recombination deficiency scores (*P* = .00013). Large-scale state transitions were the primary discriminating feature (*P* = .001); neither mutational burden nor neoantigen burden could explain differences in immunogenicity. In Penn tumors, *PTEN* loss and high homologous recombination deficiency cancers exhibited fewer CD3+ (*P* = .05), CD8+ (*P* = .012), and FOXP3+ (*P* = .0087) T cells; decreased PRF1 expression (*P* = .041); and lower immune costimulatory and inhibitory molecule expression.

CONCLUSION Our study suggests that within ovarian cancers with genetic loss of *BRCA1/2* are two subsets exhibiting differential immunogenicity, with lower levels associated with *PTEN* loss and BRCA hypermethylation. These genomic features of *BRCA1/2*-associated ovarian cancers may inform considerations around how to optimally deploy immune checkpoint inhibitors in the clinic.

Genomic characterization of small cell carcinomas of the uterine cervix. AM Schultheis, I de Bruijn, P Selenica, GS Macedo, EM da Silva, S Piscuoglio, AA Jungbluth, KJ Park, DS Klimstra, E Wardelmann, W Hartmann, CD Gerharz, M von Petersdorff, R Buettner, JS Reis-Filho, B Weigelt. Mol Oncol, 16: 833-845. https://doi.org/10.1002/1878-0261.12962

Small cell carcinoma (SCC) of the uterine cervix is a rare and aggressive form of neuroendocrine carcinoma, which resembles small cell lung cancer (SCLC) in its histology and poor survival rate. Here, we sought to define the genetic underpinning of SCCs of the uterine cervix and compare their mutational profiles with those of human papillomavirus (HPV)-positive head and neck squamous cell carcinomas, HPV-positive cervical carcinomas, and SCLCs using publicly available data. Using a combination of whole-exome and targeted massively parallel sequencing, we found that the nine uterine cervix SCCs, which were HPV18-positive (n = 8) or HPV16-positive (n = 1), harbored a low mutation burden, few copy number alterations, and other than TP53 in two cases no recurrently mutated genes. The majority of mutations were likely passenger missense mutations, and only few affected previously described cancer-related genes. Using RNA-sequencing, we identified putative viral integration sites on 18q12.3 and on 8p22 in two SCCs of the uterine cervix. The overall nonsilent mutation rate of uterine cervix SCCs was significantly lower than that of SCLCs, HPV-driven cervical adeno- and squamous

cell carcinomas, or HPV-positive head and neck squamous cell carcinomas. Unlike SCLCs, which are reported to harbor almost universal TP53 and RB1 mutations and a dominant tobacco smoke-related signature 4, uterine cervix SCCs rarely harbored mutations affecting these genes (2/9, 22% TP53; 0% RB1) and displayed a dominant aging (67%) or APOBEC mutational signature (17%), akin to HPV-driven cancers, including cervical adeno- and squamous cell carcinomas and head and neck squamous cell carcinomas. Taken together, in contrast to SCLCs, which are characterized by highly recurrent TP53 and RB1 alterations, uterine cervix SCCs were positive for HPV leading to inactivation of the suppressors p53 and RB, suggesting that these SCCs are convergent phenotypes.

The Molecular Tumor Board Portal supports clinical decisions and automated reporting for precision oncology. D Tamborero, R Dienstmann, MH Rachid, J Boekel, A Lopez-Fernandez, M Jonsson, A Razzak, I Braña, L De Petris, J Yachnin, RD Baird, Y Loriot, C Massard, P Martin-Romano, F Opdam, RF Schlenk, C Vernieri, M Masucci, X Villalobos, E Chavarria, Cancer Core Europe consortium, J Balmaña, Giovanni Apolone, Carlos Caldas, Jonas Bergh, Ingemar Ernberg, Stefan Fröhling, Elena Garralda, C Karlsson, J Tabernero, E Voest, J Rodon, J Lehtiö Nature Cancer 3, 251–261 (2022). https://doi.org/10.1038/s43018-022-00332-x

There is a growing need for systems that efficiently support the work of medical teams at the precision-oncology point of care. Here, we present the implementation of the Molecular Tumor Board Portal (MTBP), an academic clinical decision support system developed under the umbrella of Cancer Core Europe that creates a unified legal, scientific and technological platform to share and harness next-generation sequencing data. Automating the interpretation and reporting of sequencing results decrease the need for time-consuming manual procedures that are prone to errors. The adoption of an expert-agreed process to systematically link tumor molecular profiles with clinical actions promotes consistent decision-making and structured data capture across the connected centers. The use of information-rich patient reports with interactive content facilitates collaborative discussion of complex cases during virtual molecular tumor board meetings. Overall, streamlined digital systems like the MTBP are crucial to better address the challenges brought by precision oncology and accelerate the use of emerging biomarkers.

Performance of DNA methylation analysis of ASCL1, LHX8, ST6GALNAC5, GHSR, ZIC1 and SST for the triage of HPV-positive women: Results from a Dutch primary HPV-based screening cohort. L Verhoef, MCG Bleeker, N Polman, RDM Steenbergen, CJL M. Meijer, WJG Melchers, RL Bekkers, AC Molijn, WG Quint, FJ van Kemenade, J Berkhof, DAM Heideman. *Int. J. Cancer*. 2022; 150(3): 440- 449. doi:10.1002/ijc.33820

Abstract

Methylation of host-cell deoxyribonucleic acid (DNA) has been proposed as a promising biomarker for triage of high-risk (hr) human papillomavirus (HPV) positive women at screening. Our study aims to validate recently identified host-cell DNA methylation markers for triage in an hrHPV-positive cohort derived from primary HPV-based cervical screening in The Netherlands. Methylation markers *ASCL1, LHX8, ST6GALNAC5, GHSR, ZIC1* and *SST* were evaluated relative to the *ACTB* reference gene by multiplex quantitative methylation-specific PCR (qMSP) in clinician-collected cervical samples (n = 715) from hrHPV-positive women (age 29-60 years), who were enrolled in the Dutch IMPROVE screening trial (NTR5078). Primary clinical end-point was cervical intraepithelial neoplasia grade 3 (CIN3) or cancer (CIN3+). The single-marker and bi-marker methylation classifiers developed for CIN3 detection in a previous series of hrHPV-positive clinician-collected cervical samples were applied. The diagnostic accuracy was visualized using receiver operating characteristic (ROC) curves and assessed through area under the ROC curve (AUC). The performance of the methylation markers to detect CIN3+ was determined using the predefined threshold calibrated at 70% clinical specificity. Individual methylation makers showed good performance for CIN3+ detection, with highest AUC for *ASCL1* (0.844) and *LHX8* (0.830). Combined as a bi-marker panel with predefined threshold, *ASCL1/LHX8* yielded a CIN3+ sensitivity of 76.9% (70/91; 95% CI 68.3-85.6%) at a specificity of 74.5% (465/624; 95% CI 71.1-77.9%). In conclusion, our study shows that the individual host-cell DNA methylation classifiers and the bi-marker panel *ASCL1/LHX8* have clinical utility for the detection of CIN3+ in hrHPV-positive women invited for routine screening.

What's new?

As cervical screening transitions from cytology to primary human papillomavirus (HPV) testing worldwide, effective triage tests are increasingly needed. Here, the authors report on the performance of host-cell DNA methylation biomarkers *ASCL1*, *LHX8*, *ST6GALNAC5*, *GHSR*, *ZIC1*, and *SST* in an HPV-positive cohort derived from primary HPV-based screening in The Netherlands. All markers exhibited significant differences in methylation levels between cervical intraepithelial neoplasia grade 3 or worse (CIN3/CIN3+) and CIN1, CIN2, and women with normal histology. The robust triage performance for CIN3+ as compared to cytology and HPV16/18 genotyping highlights the potential of methylation biomarker-based triage for HPV-positive women.

Clinical validation of p16/Ki-67 dual-stained cytology triage of HPV-positive women: Results from the IMPACT trial. TC Wright Jr, MH Stoler, J Ranger-Moore, Q Fang, P Volkir, M Safaeian, R Ridder. Int. J. Cancer. 2022; 150(3): 461- 471. doi:10.1002/ijc.33812 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33812

Abstract

Triage strategies are needed for primary human papillomavirus (HPV)-based cervical cancer screening to identify women requiring colposcopy/biopsy. We assessed the performance of p16/Ki-67 dual-stained (DS) immunocytochemistry to triage HPV-positive women and compared it to cytology, with or without HPV16/18 genotyping. A prospective observational screening study enrolled 35 263 women aged 25 to 65 years at 32 U.S. sites. Cervical samples had HPV and cytology testing, with colposcopy/biopsy for women with positive tests. Women without cervical intraepithelial neoplasia Grade 2 or worse (≥CIN2) at baseline (n = 3876) were retested after 1 year. In all, 4927 HPV-positive women with valid DS results were included in this analysis. DS sensitivity for ≥CIN2 and ≥CIN3 at baseline was 91.2% (95% confidence interval [CI]: 86.8%-94.2%) and 91.9% (95% CI: 86.1%-95.4%), respectively, in HPV16/18-positive women and 83.0% (95% CI: 78.4%-86.8%) and 86.0% (95% CI: 77.5%-91.6%) in women with 12 "other" genotypes. Using DS alone to triage HPV-positive women showed significantly higher sensitivity and specificity than HPV16/18 genotyping with cytology triage of 12 "other" genotypes, and substantially higher sensitivity but lower specificity than using cytology alone. The risk of ≥CIN2 was significantly lower in HPV-positive, DS-negative women (3.6%; 95% CI: 2.9%-4.4%), compared to triage-negative women using HPV16/18 genotyping with cytology for 12 "other" genotypes (7.4%; 95% CI: 6.4%-8.5%; *P* < .0001) or cytology alone (7.5%; 95% CI: 6.7%-8.4%; *P* < .0001). DS showed better risk stratification than cytology-based strategies and provided high reassurance against pre-cancers both at baseline and at 1-year follow-up, irrespective of the HPV genotype. DS allows for the safe triage of primary screening HPV-positive women.

Abstract

What's new?

Primary screening for human papillomavirus (HPV) requires efficient triage of HPV-positive women to colposcopy and biopsy. In this prospective observational trial in the United States, with 1-year longitudinal follow-up, the authors investigated the performance of p16/Ki-67 dual-stain cytology for the triage of women identified as HPV-positive during primary screening. Compared to HPV16/18 genotyping combined with cytological triage of other HPV genotypes, dual-stain cytology was significantly more sensitive for predicting risk of cervical intraepithelial neoplasia grade 2/3 or worse. The findings indicate that dual-stain cytology is effective for triage of HPV-positive women, either alone or when combined with partial HPV genotyping.

Senescence induction dictates response to chemo- and immunotherapy in preclinical models of ovarian cancer. SV Paffenholz, C Salvagno, Y-J Ho, M Limjoco, Timour Baslan, Sha Tian, A Kulick, E de Stanchina, JE Wilkinson, FM Barriga, D Zamarin, JR Cubillos-Ruiz, J Leibold, and SW Lowe. PNAS 119 (5) e2117754119 https://doi.org/10.1073/pnas.2117754119

Significance

Efforts to understand and find new treatment options for high-grade serous ovarian cancer (HGSOC) have been confounded by a paucity of immune-competent models that accurately reflect the genetics and biology of the disease. Here, we leverage somatic tissue engineering to develop a fast and flexible immune-competent mouse model of HGSOC and reveal mechanistic insights into factors that dictate the response of ovarian tumors to conventional chemotherapy and immune checkpoint blockade. Our results identify a genotype-dependent therapy-induced senescence program that mediates sensitivity and resistance to first line chemotherapy and point to strategies to harness the senescence program to sensitize ovarian tumors to immune checkpoint blockade.

Abstract

High-grade serous ovarian carcinoma (HGSOC) is a cancer with dismal prognosis due to the limited effectiveness of existing chemo- and immunotherapies. To elucidate mechanisms mediating sensitivity or resistance to these therapies, we developed a fast and flexible autochthonous mouse model based on somatic introduction of HGSOC-associated genetic alterations into the ovary of immunocompetent mice using tissue electroporation. Tumors arising in these mice recapitulate the metastatic patterns and histological, molecular, and treatment response features of the human disease. By leveraging these models, we show that the ability to undergo senescence underlies the clinically observed increase in sensitivity of homologous recombination (HR)–deficient HGSOC tumors to platinum-based chemotherapy. Further, cGas/STING-mediated activation of a restricted senescence-associated secretory phenotype (SASP) was sufficient to induce immune infiltration and sensitize HR-deficient tumors to immune checkpoint blockade. In sum, our study identifies senescence propensity as a predictor of therapy response and defines a limited SASP profile that appears sufficient to confer added vulnerability to concurrent immunotherapy and, more broadly, provides a blueprint for the implementation of electroporation-based mouse models to reveal mechanisms of oncogenesis and therapy response in HGSOC.

Predicting regression of cervical intraepithelial neoplasia grade 2 in women under 25 years. PH Sykes, BJ Simcock, CR Innes, D Harker, JA. Williman, M Whitehead, RA van der Griend, BA Lawton, M Hibma, P Fitzgerald, NM Dudley, S Petrich, L Eva, C Bergzoll, J Kathuria, G McPherson, A Tristram, J Faherty, D Hardie, A Robertson,

V Robertson, S Pather, CD Wrede, F Gastrell, G Fentiman, M John, E White, C Parker, L Sadler. American Journal of Obstetrics and Gynecology. 226, (2) 2022, 222.e1-222.e13, https://doi.org/10.1016/j.ajog.2021.09.009. https://www.sciencedirect.com/science/article/pii/S0002937821010061?via%3Dihub

Background A number of retrospective and prospective studies have documented substantial rates of regression in cervical intraepithelial neoplasia grade 2 lesions in young women. Initial observational management of cervical intraepithelial neoplasia grade 2 is increasingly accepted as appropriate for women under 25 years of age with screen-detected abnormalities and is included in a number of clinical guidelines. However, there has been a paucity of large prospective studies on observational management with strict inclusion criteria. A number of important questions remain, specifically regarding the clinical variables that are associated with the risk of progression or persistence of disease. To investigate these factors and to ensure that young women with cervical intraepithelial neoplasia grade 2 undergoing observational management were being managed in a well-monitored and an appropriately informed fashion, we conducted a large, multicenter prospective study on observational management of cervical intraepithelial neoplasia grade 2 in women under 25 years.

Objective This study aimed to determine the regression rates and clinical, cytologic, and pathologic predictors of regression of cervical intraepithelial neoplasia grade 2 in women under 25 years undergoing observational management over 24 months.

Study Design This study was a multicenter prospective study on observational management of cervical intraepithelial neoplasia grade 2 (ie, repeat colposcopy, cytology, and cervical biopsy every 6 months) for up to 24 months. A total of 615 consenting women under 25 years with newly-diagnosed, biopsy-proven cervical intraepithelial neoplasia grade 2 were recruited (from 2010 to 2016) through 16 hospital-based colposcopy units in New Zealand and Australia.

Results At completion, 326 women had confirmed regression, 156 had persistent high-grade cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ, and 24 had unconfirmed regression (ie, first regression at the 24-month follow-up). A total of 109 women did not complete the protocol (41 because of delayed follow-up, 41 lost to follow-up, 22 elected treatment, 4 refused a biopsy, and 1 died of an unrelated cause). Confirmed regression was observed in 53% (326 of 615) of all women enrolled in the study and, when missing data were imputed, it was estimated that 64% of women (95% confidence interval, 60%–68%) would have experienced regression. Similarly, lesions regressed in 64% (326 of 506) of women who completed the observational protocol. Based on a multivariable analysis, detection of human papillomavirus 16 in a liquid-based cytology sample at the time of initial colposcopy decreased the chance of regression by 31% (risk ratio, 0.69; 95% confidence interval, 0.56–0.86; P<.001). In addition, at initial colposcopy, low-grade or normal colposcopic impression, later year of diagnosis, low-grade or normal cytology, and being a nonsmoker were all independently associated with an increased chance of regression.

Conclusion More than half of women under 25 years with cervical intraepithelial neoplasia grade 2 will regress to cervical intraepithelial neoplasia grade 1 or normal within 24 months without destructive treatment. The absence of human papillomavirus 16 is the most important predictor of regression.

Ovarian cancer incidence and death in average-risk women undergoing bilateral salpingo-oophorectomy at benign hysterectomy. MC Cusimano, SE Ferguson, R Moineddin, M Chiu, S Aktar, N Liu, NN Baxter. American Journal of Obstetrics and Gynecology, 226, (2) 2022, 220.e1-220.e26, https://doi.org/10.1016/j.ajog.2021.09.020. https://www.sciencedirect.com/science/article/pii/S0002937821010486?via%3Dihub

Background Opportunistic bilateral salpingo-oophorectomy is often offered to patients undergoing benign hysterectomy to prevent ovarian cancer, but the magnitude of risk reduction obtained with bilateral salpingo-oophorectomy in this population remains unclear and must be weighed against potential risks of ovarian hormone deficiency.

Objective This study aimed to quantify the relative and absolute risk reduction in ovarian cancer incidence and death associated with bilateral salpingo-oophorectomy at the time of benign hysterectomy.

Study Design We performed a population-based cohort study of all adult women (≥20 years) undergoing benign hysterectomy from 1996 to 2010 in Ontario, Canada. Patients with ovarian pathology, previous breast or gynecologic cancer, or evidence of genetic susceptibility to malignancy were excluded. Inverse probability of treatment–weighted Fine-Gray subdistribution hazard models were used to quantify the effect of bilateral salpingo-oophorectomy on ovarian cancer incidence and death while accounting for competing risks and adjusting for demographic characteristics, gynecologic conditions, and comorbidities. Analyses were performed in all women and specifically in women of postmenopausal age (≥50 years) at the time of hysterectomy.

Results We identified 195,282 patients (bilateral salpingo-oophorectomy, 24%; ovarian conservation, 76%) with a median age of 45 years (interquartile range, 40–51 years). Over a median follow-up of 16 years (interquartile range, 12–20 years), 548 patients developed ovarian cancer (0.3%), and 16,170 patients (8.3%) died from any cause. Bilateral salpingo-oophorectomy was associated with decreased ovarian cancer incidence (hazard ratio, 0.23; 95% confidence interval, 0.14–0.38; *P*<.001) and decreased ovarian cancer death (hazard ratio, 0.30; 95% confidence interval, 0.16–0.57; *P*<.001). At 20 years follow-up, the weighted cumulative incidences of ovarian cancer were 0.08% and 0.46% with bilateral salpingo-oophorectomy and ovarian conservation, respectively, yielding an absolute risk reduction of 0.38% (95% confidence

interval, 0.32–0.45; number needed to treat, 260). After restricting to women aged ≥50 years at hysterectomy, the absolute risk reduction was 0.62% (95% confidence interval, 0.47–0.77; number needed to treat, 161).
Conclusion Bilateral salpingo-oophorectomy resulted in a significant absolute reduction in ovarian cancer among women undergoing benign hysterectomy. Population-average risk estimates derived in this study should be balanced against other potential implications of bilateral salpingo-oophorectomy to inform practice guidelines, patient decision-making, and surgical management.

Survival with Cemiplimab in Recurrent Cervical Cancer. KS Tewari, BJ Monk, I Vergote, A Miller, AC de Melo, H-S Kim, YM Kim, A Lisyanskaya, V Samouëlian, D Lorusso, F Damian, C-L Chang. N Engl J Med 2022; 386:544-555 DOI: 10.1056/NEJMoa2112187 https://www.nejm.org/doi/full/10.1056/NEJMoa2112187
BACKGROUND Patients with recurrent cervical cancer have a poor prognosis. Cemiplimab, the fully human programmed cell death 1 (PD-1)–blocking antibody approved to treat lung and skin cancers, has been shown to have preliminary clinical activity in this population.
METHODS In this phase 3 trial, we enrolled patients who had disease progression after first-line platinum-containing chemotherapy, regardless of their programmed cell death ligand 1 (PD-L1) status. Women were randomly assigned (1:1) to receive cemiplimab (350 mg every 3 weeks) or the investigator's choice of single-agent chemotherapy. The primary end point was overall survival. Progression-free survival and safety were also assessed.
RESULTS A total of 608 women were enrolled (304 in each group). In the overall trial population, median overall survival was longer in the cemiplimab group than in the chemotherapy group (12.0 months vs. 8.5 months; hazard ratio for death, 0.69; 95% confidence interval [CI], 0.56 to 0.84; two-sided P<0.001). The overall survival benefit was consistent in both histologic subgroups (squamous-cell carcinoma and adenocarcinoma [including adenosquamous carcinoma]). Progression-free survival was also longer in the cemiplimab group than in the chemotherapy group in the overall population (hazard ratio for disease progression or death, 0.75; 95% CI, 0.63 to 0.89; two-sided P<0.001). In the overall population, an objective response occurred in 16.4% (95% CI, 12.5 to 21.1) of the patients in the cemiplimab group, as compared with 6.3% (95% CI, 3.8 to 9.6) in the chemotherapy group. An objective response occurred in 18% (95% CI, 11 to 28) of the cemiplimab-treated patients with PD-L1 expression greater than or equal to 1% and in 11% (95% CI, 4 to 25) of those with PD-L1 expression of less than 1%. Overall, grade 3 or higher adverse events occurred in 45.0% of the patients who received cemiplimab and in 53.4% of those who received chemotherapy.
CONCLUSIONS Survival was significantly longer with cemiplimab than with single-agent chemotherapy among patients with recurrent cervical cancer after first-line platinum-containing chemotherapy.

Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. DM Gershenson, A Miller, WE Brady, J Paul, K Carty, W Rodgers, D Millan, RL Coleman, KN Moore, S Banerjee, K Connolly, Angeles Alvarez Secord, David M O'Malley, Oliver Dorigo, Stephanie Gaillard, Hani Gabra, Brian Slomovitz, Parviz Hanjani, J Farley, M Churchman, A Ewing, RL Hollis, CS Herrington, HQ Huang, L Wenzel, C Gourley. The Lancet, 399, (10324) 2022, 541-553, https://doi.org/10.1016/S0140-6736(21)02175-9. https://www.sciencedirect.com/science/article/pii/S0140673621021759?via%3Dihub
Background Low-grade serous carcinoma of the ovary or peritoneum is characterised by MAPK pathway aberrations and its reduced sensitivity to chemotherapy relative to high-grade serous carcinoma. We compared the MEK inhibitor trametinib to physician's choice standard of care in patients with recurrent low-grade serous carcinoma.
Methods This international, randomised, open-label, multicentre, phase 2/3 trial was done at 84 hospitals in the USA and UK. Eligible patients were aged 18 years or older with recurrent low-grade serous carcinoma and measurable disease, as defined by Response Evaluation Criteria In Solid Tumors version 1.1, had received at least one platinum-based regimen, but not all five standard-of-care drugs, and had received an unlimited number of previous regimens. Patients with serous borderline tumours or tumours containing low-grade serous and high-grade serous carcinoma were excluded. Eligible patients were randomly assigned (1:1) to receive either oral trametinib 2 mg once daily (trametinib group) or one of five standard-of-care treatment options (standard-of-care group): intravenous paclitaxel 80 mg/m^2 by body surface area on days 1, 8, and 15 of every 28-day cycle; intravenous pegylated liposomal doxorubicin 40–50 mg/m^2 by body surface area once every 4 weeks; intravenous topotecan 4 mg/m^2 by body surface area on days 1, 8, and 15 of every 28-day cycle; oral letrozole 2·5 mg once daily; or oral tamoxifen 20 mg twice daily. Randomisation was stratified by geographical region (USA or UK), number of previous regimens (1, 2, or ≥3), performance status (0 or 1), and planned standard-of-care regimen. The primary endpoint was investigator-assessed progression-free survival while receiving randomised therapy, as assessed by imaging at baseline, once every 8 weeks for 15 months, and then once every 3 months thereafter, in the intention-to-treat population. Safety was assessed in patients who received at least one dose of study therapy. This trial is registered with ClinicalTrials.gov, NCT02101788, and is active but not recruiting.
Findings Between Feb 27, 2014, and April 10, 2018, 260 patients were enrolled and randomly assigned to the trametinib group (n=130) or the standard-of-care group (n=130). At the primary analysis, there were 217 progression-free survival events (101 [78%] in the trametinib group and 116 [89%] in the standard-of-care group). Median progression-free survival

in the trametinib group was 13·0 months (95% CI 9·9–15·0) compared with 7·2 months (5·6–9·9) in the standard-of-care group (hazard ratio 0·48 [95% CI 0·36–0·64]; p<0·0001). The most frequent grade 3 or 4 adverse events in the trametinib group were skin rash (17 [13%] of 128), anaemia (16 [13%]), hypertension (15 [12%]), diarrhoea (13 [10%]), nausea (12 [9%]), and fatigue (ten [8%]). The most frequent grade 3 or 4 adverse events in the standard-of-care group were abdominal pain (22 [17%]), nausea (14 [11%]), anaemia (12 [10%]), and vomiting (ten [8%]). There were no treatment-related deaths. **Interpretation** Trametinib represents a new standard-of-care option for patients with recurrent low-grade serous carcinoma.

RE: Endometrial Cancer Risk in Women With Germline *BRCA1* or *BRCA2* Mutations: Multicenter Cohort Study. C Nahshon, O Lavie. *JNCI: Journal of the National Cancer Institute*, Volume 114, Issue 2, February 2022, Pages 320–321, https://doi.org/10.1093/jnci/djab154 https://academic.oup.com/jnci/article/114/2/320/6356525

In this issue of the Journal, we have read the article by De Jonge et al. and the editorial remarks by Sherman et al. with great interest and compliment the authors on this important research and comments. In accordance with our recently published meta-analysis 3), the authors found a 2- to 3-fold increased endometrial cancer EC) risk in *BRCA1/2* mutated patients and an especially higher 12- to 13-fold) risk for uterine serous cancer USC).

The study by De Jonge et al. adds to the evidence-based clinicians' discussion with *BRCA1/2* mutated patients regarding EC risk. As more studies have shown that EC in general, and USC in particular, may be part of the *BRCA1/2* syndrome, awareness of this risk may affect EC prevention, detection, and management.

Although not recommended by De Jonge et al., in our opinion, risk reduction hysterectomy should be discussed with every woman with a *BRCA1/2* mutation scheduled for risk reduction bilateral salpingo-oophorectomy. Even with low absolute risks of USC, all patients should be aware of the risk addition due to their *BRCA1/2* mutation, as USC is an aggressive EC subtype responsible for 40% of deaths from the disease. The decision of performing risk reduction hysterectomy at the time of risk reduction bilateral salpingo-oophorectomy should be individualized. Advantages such as elimination of EC risk, especially when in need for future tamoxifen or hormonal treatment, should be considered alongside the disadvantages and morbidities of a more complex surgery.

Tamoxifen treatment has been thought to be a key player in the elevated EC rates in breast cancer BC) survivors. However, whether this increased risk is attributed solely to tamoxifen treatment or to a similar genetic predisposition is not well established. Tamoxifen has been shown to increase the risk for EC in BC survivors, however, studies have shown increased rates of EC even in patients with estrogen receptor–negative BC. The current study by De Jonge et al. presented that the increased risk of EC in *BRCA1/2* was found regardless of tamoxifen treatment and further supports that USC may be truly considered part of the *BRCA1/2* syndrome.

The association between *BRCA1/2* mutations and USC may imply that systemic treatments used for ovarian cancer *BRCA1/2* mutated patients, such as poly-ADP ribose polymerase inhibitors PARPi), might be efficient in the treatment of USC. Since introducing PARPi as a treatment for ovarian cancer, several studies have been conducted to assess the efficacy of PARPi treatment in other gyneco-oncological cancer including EC. In addition to the studied similar genetic basis of ovarian cancer and USC, it has been shown that homologous recombination deficiency HRD) was statistically significantly associated with nonendometroid histologies of EC, thus possibly suspectable to PARPi. Although no conclusions have yet been published, it is assumed that as PARPi were shown effective in *BRCA1/2* and HRD ovarian cancer patients, USC patients with germline or somatic *BRCA* mutation or HRD will also benefit from PARPi treatment.

Ongoing clinical trials are now studying PARPi in EC management, and these results will further establish the clinical association between *BRCA1/2* mutations and USC.

Association of Genetic Testing Results With Mortality Among Women With Breast Cancer or Ovarian Cancer. AW Kurian, P Abrahamse, I Bondarenko, AS Hamilton, D Deapen, SL Gomez, M Morrow, JS Berek, TP Hofer, SJ Katz, KC Ward, *JNCI: Journal of the National Cancer Institute*, Volume 114, Issue 2, February 2022, Pages 245–253, https://doi.org/10.1093/jnci/djab151 https://academic.oup.com/jnci/article-abstract/114/2/245/6346986?redirectedFrom=fulltext

Background Breast cancer and ovarian cancer patients increasingly undergo germline genetic testing. However, little is known about cancer-specific mortality among carriers of a pathogenic variant PV) in *BRCA1/2* or other genes in a population-based setting.

Methods Georgia and California Surveillance Epidemiology and End Results SEER) registry records were linked to clinical genetic testing results. Women were included who had stages I-IV breast cancer or ovarian cancer diagnosed in 2013-2017, received chemotherapy, and were linked to genetic testing results. Multivariable Cox proportional hazard models were used to examine the association of genetic results with cancer-specific mortality.

Results 22 495 breast cancer and 4320 ovarian cancer patients were analyzed, with a median follow-up of 41 months. PVs were present in 12.7% of breast cancer patients with estrogen and/or progesterone receptor-positive, HER2-negative cancer, 9.8% with HER2-positive cancer, 16.8% with triple-negative breast cancer, and 17.2% with ovarian cancer. Among triple-negative breast cancer patients, cancer-specific mortality was lower with *BRCA1* hazard ratio [HR] = 0.49, 95% confidence interval [CI] = 0.35 to 0.69) and *BRCA2* PVs HR = 0.60, 95% CI = 0.41 to 0.89), and equivalent with PVs in other

genes HR = 0.65, 95% CI = 0.37 to 1.13), vs noncarriers. Among ovarian cancer patients, cancer-specific mortality was lower with PVs in *BRCA2* HR = 0.35, 95% CI = 0.25 to 0.49) and genes other than *BRCA1/2* HR = 0.47, 95% CI = 0.32 to 0.69). No PV was associated with higher cancer-specific mortality.

Conclusions Among breast cancer and ovarian cancer patients treated with chemotherapy in the community, *BRCA1/2* and other gene PV carriers had equivalent or lower short-term cancer-specific mortality than noncarriers. These results may reassure newly diagnosed patients, and longer follow-up is ongoing.

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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).