In The Know

Gyn Onc Literature of Significance

Ed's List
March 2022

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

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March

Clinically translatable cytokine delivery platform for eradication of intraperitoneal tumors. AM Nash, I JARVIS, S AGHLARA-FOTOVAT, S MUKHERJEE, A HERNANDEZ, AD HECHT, PD RIOS, S GHANIIRA, I JOSHI, O VEISEH. Science Advances (2022). DOI: 10.1126/sciadv.abm1032. https://www.science.org/doi/10.1126/sciadv.abm1032

(*This is a report on implantable drug factories that can eradicate advanced-stage ovarian and colorectal cancer in mice in as little as six days. The factories are the size of a pin head and consist of cells engineered to produce interleukin-2 that are encased in a protective shell*)

Proinflammatory cytokines have been approved by the Food and Drug Administration for the treatment of metastatic melanoma and renal carcinoma. However, effective cytokine therapy requires high-dose infusions that can result in antidrug antibodies and/or systemic side effects that limit long-term benefits. To overcome these limitations, we developed a clinically translatable cytokine delivery platform composed of polymer-encapsulated human ARPE-19 (RPE) cells that produce natural cytokines. Tumor-adjacent administration of these capsules demonstrated predictable dose modulation with spatial and temporal control and enabled peritoneal cancer immunotherapy without systemic toxicities. Interleukin-2 (IL2)–producing cytokine factory treatment eradicated peritoneal tumors in ovarian and colorectal mouse models. Furthermore, computational pharmacokinetic modeling predicts clinical translatability to humans. Notably, this platform elicited T cell responses in NHPs, consistent with reported biomarkers of treatment efficacy without toxicity. Combined, our findings demonstrate the safety and efficacy of IL2 cytokine factories in preclinical animal models and provide rationale for future clinical testing in humans.

Spatiotemporal dynamics of clonal selection and diversification in normal endometrial epithelium. M Yamaguchi, H Nakaoka, K Suda, K. et al. Nat Commun 13, 943 (2022). https://doi.org/10.1038/s41467-022-28568-2 https://www.nature.com/articles/s41467-022-28568-2

(*This paper indicates that the highly regenerating nature the endometrial endometrium can be a source of genetic mutations, increasing the likelihood of developing endometrium-related diseases, such as endometriosis, adenomyosis, endometrial hyperplasia, and endometrial cancer*.)

It has become evident that somatic mutations in cancer-associated genes accumulate in the normal endometrium, but spatiotemporal understanding of the evolution and expansion of mutant clones is limited. To elucidate the timing and mechanism of the clonal expansion of somatic mutations in cancer-associated genes in the normal endometrium, we sequence 1311 endometrial glands from 37 women. By collecting endometrial glands from different parts of the endometrium, we show that multiple glands with the same somatic mutations occupy substantial areas of the endometrium. We demonstrate that "rhizome structures", in which the basal glands run horizontally along the muscular layer and multiple vertical glands rise from the basal gland, originate from the same ancestral clone. Moreover, mutant clones detected in the vertical glands diversify by acquiring additional mutations. These results suggest that clonal expansions through the rhizome structures are involved in the mechanism by which mutant clones extend their territories. Furthermore, we show clonal expansions and copy neutral loss-of-heterozygosity events occur early in life, suggesting such events can be tolerated many years in the normal endometrium. Our results of the evolutionary dynamics of mutant clones in the human endometrium will lead to a better understanding of the mechanisms of endometrial regeneration during the menstrual cycle and the development of therapies for the prevention and treatment of endometrium-related diseases.

Perspectives on Ovarian Cancer 1809 to 2022 and Beyond. FG Lawton, EJ Pavlik. Diagnostics. 2022; 12(4):791. https://doi.org/10.3390/diagnostics12040791 https://www.mdpi.com/2075-4418/12/4/791/htm

Unlike many other malignancies, overall survival for women with epithelial ovarian cancer has improved only modestly over the last half-century. The perspectives presented here detail the views of a gynecologic oncologist looking back and the view of the academic editor looking forward. Surgical beginnings in 1809 are merged with genomics, surgical advances, and precision therapy at present and for the future. Presentations in this special issue focus on factors related to the diagnosis of ovarian cancer: (1) markers for the preoperative assessment of primary and metastatic ovarian tumors, (2) demonstrations of the presence of pelvic fluid in ultrasound studies of ovarian malignancies, (3) the effects of age, menopausal status, and body habitus on ovarian visualization, (4) the ability of OVA1 to detect ovarian cancers when Ca125 was not informative, (5) the detection of tumor-specific changes in cell adhesion molecules by tissue-based staining, (6) presentation of a high discrimination model for ovarian cancer using IOTA Simple Rules and CA125, (7) review of low-grade serous carcinoma of the ovary, and (8) a comprehensive case report on ovarian carcinosarcoma.

Risk of Peritoneal Cancer After Risk-Reducing Bilateral Salpingo-Oophorectomy for Women With Germline BRCA Pathogenic Variants: A Cause for Concern or Potentially Avoidable?

K-A Phillips, ML Friedlander. Journal of Clinical Oncology 0 0:0 https://ascopubs.org/doi/full/10.1200/JCO.22.00325?af=R

Women who carry a germline BRCA1 or BRCA2 pathogenic variant (PV) have a high lifetime risk of epithelial ovarian cancer. The average cumulative risk by age 80 years is 44% for those with a BRCA1 PV and 17% for those with a BRCA2 PV, compared with 1.3% for the general population. Most are high-grade serous cancers that appear to originate, predominantly from serous tubal intraepithelial carcinoma (STIC), in the fimbria or distal third of the fallopian tube. Pathologic studies suggest a progression from p53 over-expression (because of TP53 mutation—so-called p53 signature) to serous tubal intraepithelial lesions, through to STIC and invasive carcinoma. However, this may be an oversimplification, and there is evidence that high-grade serous cancers may arise not only from STICs but also from TP53-mutated, premalignant tubal serous proliferations, which can detach from the fallopian tube and undergo malignant transformation in the peritoneal cavity. Furthermore, to add another layer of complexity, there is evidence that in some advanced-stage serous cancers, the STIC may be a metastatic implant rather than a precursor lesion. For most women, the risk of epithelial ovarian cancer does not start to increase above that of the general population until the mid-30s in those with a BRCA1 PV and closer to age 50 years in those with a BRCA2 PV. Surgical removal of both ovaries and fallopian tubes reduces this risk dramatically, is associated with a reduction in ovarian cancer–specific mortality, and is strongly recommended between age 35-40 years and 40-45 years for BRCA1 and BRCA2 PV carriers, respectively. However, there is a small residual risk (1%-4%) for peritoneal carcinomatosis after risk-reducing bilateral salpingo-oophorectomy (rrBSO), which should be discussed during counseling before surgery.

In the article that accompanies this editorial, Steenbeek et al (https://ascopubs.org/doi/full/10.1200/JCO.21.02016) show that the presence of STIC at the time of rrBSO was strongly associated with the subsequent development of peritoneal carcinomatosis in BRCA1 and BRCA2 PV carriers. Diagnostic criteria for STIC are based on tubal morphology, abnormal p53 immunohistochemical staining, and high Ki67 staining. STICs are more commonly identified when rrBSO specimens are subjected to detailed examination of the tubal fimbriae using the Sectioning and Extensively Examining the Fimbriated end of the fallopian tube (SEE-FIM) protocol.

Steenbeek et al used pooled published and unpublished individual participant data from 3,121 women with a BRCA1 or BRCA2 PV, 115 (3.7%) of whom had an isolated STIC reported at rrBSO. Overall, 33 women (1.1%) developed peritoneal carcinomatosis over a median follow-up of 52 months, 15 of whom had STIC reported in their rrBSO specimen. The hazard ratio for subsequent peritoneal carcinomatosis for women with STIC, compared with those without, was 33.9 (95% CI, 15.6 to 73.9). The 5-year and 10-year risks for peritoneal carcinomatosis for women with STIC were 10.5% (95% CI, 6.2 to 17.2) and 27.5% (95% CI, 16.6 to 43.9), respectively, compared with 0.3% (95% CI, 0.2 to 0.6) and 0.9% (95% CI, 0.6 to 1.4), respectively, for those without STIC at rrBSO.

Previous studies have reported a prevalence of isolated STIC at rrBSO of 0.4%-11% for BRCA1 and BRCA2 PV carriers. 13 The study by Steenbeek et al 10 is consistent with those previous studies; the prevalence of STIC was 3.7%, and women diagnosed with a STIC were older at the time of their rrBSO (median age at rrBSO 52 years v 46 years) and more likely to carry a BRCA1 PV. In a Cox regression model that included age at rrBSO and BRCA type, the presence of STIC at the time of rrBSO was the only factor that was independently associated with the development of peritoneal carcinomatosis.

It is difficult to study an uncommon disease like peritoneal carcinomatosis in BRCA1 and BRCA2 PV carriers, and the existing literature consists mainly of small retrospective series. The authors have made a major effort to pull together global individual patient data, but their study findings are still based on a small number of peritoneal carcinomatosis events, resulting in risk estimates with wide CIs. The authors appropriately tried to mitigate the risk of publication bias by including the gray literature in their search strategy. However, it is still possible that studies that did not show a higher risk of peritoneal carcinomatosis in women with isolated STIC might have gone unreported and therefore will not have been included in the study by Steenbeek et al. 10 Given the retrospective nature of the data, there is also the possibility of detection bias if the assessment of STIC was not always blinded to the peritoneal carcinomatosis outcome. In data sets derived from existing databases, it might have been difficult to clearly distinguish STIC diagnosed at the time of the original rrBSO diagnostic

pathology from those diagnosed in retrospect at a later, more intensive, pathology review triggered by a peritoneal carcinomatosis diagnosis. In addition, the possibility of nonrandom loss to follow-up must be considered. If patients with STIC were followed more closely than those without STIC, they might have been more likely to have their subsequent peritoneal carcinomatosis recorded in the institutional database than those who were no longer being closely followed at the original institution and who therefore might have been treated elsewhere for their subsequent peritoneal carcinomatosis. Publication bias, detection bias, and nonrandom loss to follow-up, if present in the study by Steenbeek et al, 10 could spuriously inflate the association between the presence of STIC in the rrBSO specimen and subsequent development of peritoneal carcinomatosis. The possibility of measurement error for the STIC exposure is another potential limitation. Some patients might not have undergone complete rrBSO or standardized tissue processing with SEE-FIM (particularly those who had surgery many years ago), and there was no central pathology review of rrBSO specimens and no standardized central study definition of STIC. The pathogenesis of peritoneal carcinomatosis after rrBSO is uncertain. An association between the presence of STIC at the time of rrBSO and subsequent development of peritoneal carcinomatosis in BRCA1 or BRCA2 PV carriers is biologically plausible. STIC could represent a precursor lesion with metastatic potential that exfoliates into the peritoneal cavity at, or before, the time of rrBSO and results in peritoneal carcinoma years later. Indeed, evolutionary analyses have suggested a window of 7 years between the development of a STIC and initiation of an invasive cancer. 16 The median time between rrBSO and diagnosis of peritoneal carcinomatosis in women with STIC in the study by Steenbeek et al 10 was 48 months (range 18-118 months), which would support this hypothesis. In addition, two BRCA1 PV carriers had identical TP53 somatic mutations in their isolated STIC and subsequent peritoneal carcinomatosis that developed many years later, suggesting clonal evolution. 17 An alternative hypothesis, that the subsequent peritoneal carcinomatosis is secondary to an invasive carcinoma that was not detected at the rrBSO, seems far less likely given the often lengthy time interval seen between detection of STIC and development of peritoneal carcinomatosis. Another potential hypothesis is that the presence of STIC could merely be a marker of higher risk for peritoneal carcinomatosis, without being a precursor lesion per se. So how do the data from Steenbeek et al assist clinicians and the women they care for? First, these data are very reassuring that the risk of subsequent peritoneal carcinomatosis for women without STIC at the time of rrBSO is very low (0.9% at 10 years). For the approximately 3% of BRCA1 or BRCA2 PV carriers who have STIC at rrBSO, the situation is more complicated. Although they do appear to have an increased risk of peritoneal carcinomatosis, there is considerable uncertainty regarding optimal management of patients with a STIC. While acknowledging the limited and low-level evidence, European Society for Medical Oncology–European Society of Gynaecological Oncology consensus recommendations state that peritoneal restaging should be considered and that adjuvant chemotherapy is not recommended for isolated STIC. The role of close surveillance can also be questioned. What is clear is that timely rrBSO at the age recommended in guidelines is important, not only to reduce the potential risk for epithelial ovarian cancer but also to reduce the risk of STIC and potentially subsequent peritoneal carcinomatosis. This study also highlights the need for expert pathology evaluation of rrBSO specimens using the SEE-FIM protocol. It is important that surgeons undertaking rrBSOs in women with BRCA1 and BRCA2 PVs ensure that the high-risk status of the patient is clearly communicated on the pathology request and that the surgical specimen is examined using SEE-FIM by an expert pathologist, especially as these women are also at risk of having an occult invasive carcinoma at the time of rrBSO, which could be missed.

The study by Steenbeek et al provides important new information that the finding of isolated STIC at the time of rrBSO is a predictor of risk for subsequent peritoneal carcinomatosis. However, it will generate complex conversations between clinicians and their patients, given the current high level of uncertainty about the best way to mitigate the risk of peritoneal carcinomatosis after a diagnosis of isolated STIC, and this should be a catalyst for further research.

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ePO61: Genetic risk for breast and ovarian cancer in a diverse and unselected population.

E Soper, B Dubois, G Belbin, E Kenny, N Abul-Husn. Genetics in Medicine 24 (3) 2022, S39-S40,
https://doi.org/10.1016/j.gim.2022.01.099. https://www.gimjournal.org/action/showPdf?pii=S1098-3600%2822%2900115-0

Introduction A clear picture of the genetic architecture of breast cancer risk is taking shape since the advent of multi-gene panel testing, with damaging variants in a set of DNA repair genes now firmly established as having high (>5-fold risk) or moderate (2-5-fold risk) penetrance for this cancer. A subset of these variants also increase the risk for ovarian cancer. Identification of individuals at increased genetic risk for these cancers creates an opportunity to improve health outcomes through interventions aimed at prevention or early diagnosis and treatment. Here, we evaluated the prevalence and impact on time to cancer diagnosis of expected pathogenic variants in 14 high and moderate penetrance breast and ovarian cancer risk genes in an ancestrally diverse patient population.

Methods The Bio*Me* Biobank is an electronic health record (EHR)-linked biobank with over 60,000 participants enrolled non-selectively from ambulatory care practices across the Mount Sinai Health System in New York, NY. From exome sequence data available for 30,223 adult Bio*Me* participants, we identified expected pathogenic variants in *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11,* and *TP53*. These included ClinVar pathogenic and likely pathogenic (P/LP) variants, conflicting ClinVar variants with majority P/LP assertions, and additional predicted loss-of-function variants (frameshift, stop-gain, start-loss, or variants at canonical splice acceptor or donor sites) in these genes. We estimated the prevalence of high penetrance breast (*BRCA1, BRCA2, CDH1, PTEN, STK11, TP53*), moderate penetrance breast (*ATM, BARD1, BRIP1, CHEK2, NF1, PALB2, RAD51C, RAD51D*), and ovarian (*BRCA1, BRCA2, BRIP1, PALB2, RAD51C,* and *RAD51D*) cancer gene variants in Bio*Me* overall, and across the 8 largest

population groups defined by shared recent genetic ancestry (African American and African, Ashkenazi Jewish, Non-Ashkenazi Jewish European, Filipino and Other Southeast Asian, Dominican, Ecuadorian, Puerto Rican, and Colombian and Other Central and South American).
We evaluated the clinical consequences of expected pathogenic variants in these genes in a subset of unrelated adult female participants (N=15,919) using International Classification of Disease-9/10 codes extracted from EHRs and self-reported data from Bio*Me* enrollment questionnaires. Kaplan-Meier curves were generated to estimate time to diagnosis of breast or ovarian cancer, with the age at first record (EHR or self-reported) of breast or ovarian cancer diagnosis considered the event, and censoring at current age or age 90. Hazard ratios (HRs) were generated using Cox proportional hazards models, adjusting for current age, self-reported race and ethnicity, and the first 5 principal components of ancestry.
Results We identified 667 variant-positive individuals with 292 unique expected pathogenic variants in high or moderate penetrance breast cancer genes. The estimated prevalence of expected pathogenic variants in these genes in a subset of sequenced individuals that excluded second degree relatives or closer (N = 27,816) was 1 in 44 (Table). Across population groups defined by shared recent genetic ancestry, prevalence ranged from 1 in 21 in individuals with Ashkenazi Jewish (AJ) ancestry to 1 in 84 in those with ancestry from Puerto Rico or Ecuador (Table). At an individual gene level, *CHEK2* variants had the highest overall prevalence (1 in 140). This varied widely by genetic ancestry, with the highest prevalence observed in AJ individuals (1 in 44), largely due to overrepresentation of two low penetrance missense variants that are common in individuals of European and AJ descent (ie, c.1283C>T and c.470T>C, NM_007194.4).
We conducted survival analyses to determine if age at diagnosis differed by high or moderate penetrance breast cancer gene variant status. These analyses revealed that, by age 60, 30.7% of high penetrance variant-positive, 13.0% of moderate penetrance variant-positive, and 5.4% of variant-negative women had breast cancer. Both high and moderate penetrance variants were associated with earlier time to breast cancer diagnosis (HR = 5.8, $p = 1.2 \times 10^{-31}$; HR = 1.6, $p = 5.7 \times 10^{-3}$, respectively). The common *CHEK2* variants c.1283C>T and c.470T>C were not associated with time to breast cancer diagnosis (HR 0.81, $p = 0.6$), whereas protein-truncating and rare missense variants in this gene were associated with earlier time to breast cancer diagnosis (HR 3.2; $p = 5.6 \times 10^{-4}$). Similarly, expected pathogenic variants in the subset of ovarian cancer genes were associated with earlier time to ovarian cancer diagnosis (HR 8.3, $p = 2.5 \times 10^{-10}$), with 2.3% of variant-positive women estimated to develop ovarian cancer by age 60 compared to 0.4% of variant-negative women.
Finally, among 112 women with a documented diagnosis of ovarian cancer, we observed low rates of prior clinical genetic testing in their EHRs (18.8%). We looked at rates of genetic testing across population groups defined by self-reported race and ethnicity. The highest rates of genetic testing were in European American women at 28.6%, and lower rates were seen in Hispanic and Latina and African American-African women (17.8% and 4.2%, respectively), suggesting disparities in clinical genetic testing across population groups in women who meet clinical criteria for testing.
Conclusion These findings highlight the relevance of breast cancer genomic risk stratification to a diverse urban health care system. In aggregate, expected pathogenic variants in high and moderate penetrance breast and ovarian cancer risk genes are highly prevalent. These variants significantly reduced time to breast cancer diagnosis, with rates of diagnosis by age 60 approximately 6- and 2-fold greater in high and moderate penetrance variant-positive women respectively than in variant-negative women. However, we found no difference in time to diagnosis with common *CHEK2* missense variants, suggesting that these are of questionable clinical relevance despite routinely being reported as P/LP in clinical care. It is imperative that clinicians and patients alike be aware of the nuanced range of genomic risk to implement personalized cancer risk assessment effectively and equitably across populations.

SIK2 promotes ovarian cancer cell motility and metastasis by phosphorylating MYLK. X Shi, X Yu, J Wang, S Bian, Q Li, F Fu, X Zou, Ln Zhang, RC Bast Jr., Z Lu, L Guo, Y Chen, Ja Zhou. Mol Oncol. https://doi.org/10.1002/1878-0261.13208 https://febs.onlinelibrary.wiley.com/doi/full/10.1002/1878-0261.13208
Salt-inducible kinase 2 (SIK2; also known as serine/threonine-protein kinase SIK2) is overexpressed in several cancers and has been implicated in cancer progression. However, the mechanisms by which SIK2 regulates cancer cell motility, migration and metastasis in ovarian cancer have not been fully discovered. Here, we identify that SIK2 promotes ovarian cancer cell motility, migration and metastasis in vitro and in vivo. Mechanistically, SIK2 regulated cancer cell motility and migration by myosin light chain kinase, smooth muscle (MYLK)-meditated phosphorylation of myosin light chain 2 (MYL2). SIK2 directly phosphorylated MYLK at Ser343 and activated its downstream effector MYL2, promoting ovarian cancer cell motility and metastasis. In addition, we found that adipocytes induced SIK2 phosphorylation at Ser358 and MYLK phosphorylation at Ser343, enhancing ovarian cancer cell motility. Moreover, SIK2 protein expression was positively correlated with the expression of MYLK-pS343 in ovarian cancer cell lines and tissues. The co-expression of SIK2 and MYLK-pS343 was associated with reduced median overall survival in human ovarian cancer samples. Taken together, SIK2 positively regulates ovarian cancer motility, migration and metastasis, suggesting that SIK2 is a potential candidate for ovarian cancer treatment.

Parity is associated with better prognosis in ovarian germ cell tumors, but not in other ovarian cancer subtypes. C Sköld, A Koliadi, G Enblad, K Stålberg, I Glimelius. International J Cancer 150 (5) 2022 773-781 https://doi.org/10.1002/ijc.33844 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33844

Ovarian cancer is influenced by reproductive factors, with a reduced risk of epithelial ovarian cancer in parous women. Nonepithelial ovarian cancer frequently affects young women and often precedes or occurs during the childbearing years. However, the impact of reproductive factors on ovarian cancer survival remains unclear: in epithelial ovarian cancer, data are conflicting, and subtype-specific associations have not been examined, and in nonepithelial ovarian cancer, it has not been studied. Using Swedish registers, we evaluated associations between women's reproductive history and cancer-specific mortality by subtype of epithelial and nonepithelial ovarian cancer in 3791 women born 1953 and later, diagnosed from 1990 to 2018. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated using Cox-proportional hazard models. Parity was associated with a 78% decreased risk of cause-specific mortality in 243 women with germ cell tumors (GCTs) (parous vs nulliparous, adjusted for age at diagnosis: HR: 0.22 [95% CI 0.07-0.62]), with a decreased risk with increasing number of births (per birth: HR: 0.60 [95% CI 0.38-0.95]). We found no evidence of associations between parity and cause-specific mortality among the 334 patients with sex-cord stromal tumors, nor among the 3214 patients with epithelial ovarian cancer; neither overall, nor by subtype. In conclusion, in our large, population-based study, parity was associated with a clearly better prognosis in GCTs but not in the other ovarian cancer subtypes. Future research on how hormone exposure impacts GCT development may lead to a better understanding of mechanisms affecting survival.

What's new?

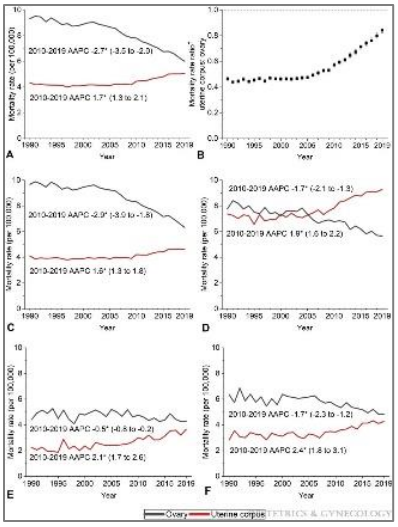
While risk of epithelial ovarian cancer is known to be influenced by pregnancy, the mechanisms underlying this association remain unclear. In this population-based study, the impact of reproductive history on ovarian cancer prognosis was evaluated by ovarian cancer subtype. Among women with germ cell tumors, parity was associated with 78 percent reduction in risk of cause-specific mortality. No associations were detected between parity and prognosis among women with sex-cord stromal tumors or epithelial ovarian cancer. These observations raise new questions about relationships between ovarian cancer prognosis and reproductive factors, including possible impacts of hormone exposure in pregnancy.

Biased Evaluation in Cancer Drug Trials—How Use of Progression-Free Survival as the Primary End Point Can Mislead. IF Tannock, GR Pond, CM Booth. JAMA Oncol. 2022. doi:10.1001/jamaoncol.2021.8206 doi:10.1001/jamaoncol.2021.8206
https://jamanetwork.com/journals/jamaoncology/article-abstract/2790095?widget=personalizedcontent&previousarticle=2785228

The goal of any cancer treatment is to improve the duration and/or quality of patient survival. In recent years, only approximately 50% of the anticancer drugs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have been shown to improve overall survival (OS) and/or a validated measure of quality of life (QoL). Most contemporary randomized clinical trials evaluating anticancer drugs use progression-free survival (PFS) as the primary end point.1 Both the FDA and EMA accept a significant improvement in PFS for the registration of drugs for most types of cancer, although PFS is rarely a surrogate for OS. Designating PFS instead of OS as the primary end point may provide results more quickly: tumors progress before patients die, so “events” occur earlier, but the reduction in study time is usually modest.2 For many new drugs that have been shown to improve PFS, subsequent analysis has demonstrated no improvement in OS or QoL, but these drugs are rarely withdrawn from the market.

The Changing Landscape of Gynecologic Cancer Mortality in the United States. AN Giaquinto, RR Broaddus, A Jemal, RL Siegel. AN Giaquinto, RR 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

In Brief Uterine corpus cancer mortality is now similar to that for ovarian cancer, and the disproportionate burden among Black women is widening.



Trends in uterine corpus and ovarian cancer mortality rates by race and ethnicity in the United States, 1990–2019. Deaths were classified according to International Classification of Diseases, Ninth Revision codes 179 and 182 for uterus and 183.0 for ovary during the years 1990–1998 and International Classification of Diseases, Tenth Revision codes C54 and C55 for uterus and C56 for ovary during the years 1999–2019. All races and ethnicities (**A**), uterus/ovary rate ratio (**B**), non-Hispanic White (**C**), non-Hispanic Black (**D**), non-Hispanic Asian/Pacific Islander (**E**), Hispanic (**F**). American Indian/Alaskan Native rates not shown owing to sparse data. Rates were age-adjusted to the 2000 U.S. standard population; data shown in **C–F** exclude Louisiana, New Hampshire, and Oklahoma owing to incomplete ethnicity information. *The average annual percent change (AAPC) was calculated using Joinpoint 4.9.0.0 based on up to 5 joinpoints, and all were statistically significantly different from 0 (two-sided *P*<.05). †Mortality rate ratio calculated using Tiwari Method.*Giaquinto. Changing Gynecologic Cancer Mortality in the United States. Obstet Gynecol 2022.*

Catastrophic health expenditures, insurance churn, and nonemployment among gynecologic cancer patients in the United States. BB Albright, R Nitecki, F Chino, JP Chino, LJ Havrilesky, EM Aviki, HA Moss. American Journal of Obstetrics and Gynecology, 226, (3), 2022, 384.e1-384.e13, https://doi.org/10.1016/j.ajog.2021.09.034. (https://www.sciencedirect.com/science/article/pii/S000293782101084X)

Background In recent years, there has been growing recognition of the financial burden of severe illness, including associations with higher rates of nonemployment, uninsurance, and catastrophic out-of-pocket health spending. Patients with gynecologic cancer often require expensive and prolonged treatments, potentially disrupting employment and insurance coverage access, and putting patients and their families at risk for catastrophic health expenditures.

Objective This study aimed to describe the prevalence of insurance churn, nonemployment, and catastrophic health expenditures among nonelderly patients with gynecologic cancer in the United States, to compare within subgroups and to other populations and assess for changes associated with the Affordable Care Act.

Study Design We identified respondents aged 18 to 64 years from the Medical Expenditure Panel Survey, 2006 to 2017, who reported care related to gynecologic cancer in a given year, and a propensity-matched cohort of patients without cancer and patients with cancers of other sites, as comparison groups. We applied survey weights to extrapolate to the US population, and we described patterns of insurance churn (any uninsurance or insurance loss or change), catastrophic health expenditures (>10% annual family income), and nonemployment. Characteristics and outcomes between groups were compared with the adjusted Wald test.

Results We identified 683 respondents reporting care related to a gynecologic cancer diagnosis from 2006 to 2017, representing an estimated annual population of 532,400 patients (95% confidence interval, 462,000–502,700). More than 64% of patients reported at least 1 of 3 primary negative outcomes of any uninsurance, part-year nonemployment, and catastrophic health expenditures, with 22.4% reporting at least 2 of 3 outcomes. Catastrophic health spending was uncommon without nonemployment or uninsurance reported during that year (1.2% of the population). Compared with patients with other cancers, patients with gynecologic cancer were younger and more likely with low education and low family income (≤250% federal poverty level). They reported higher annual risks of insurance loss (8.8% vs 4.8%; P=.03), any uninsurance (22.6% vs 14.0%; P=.002), and part-year nonemployment (55.3% vs 44.6%; P=.005) but similar risks of catastrophic spending (12.6% vs 12.2%; P=.84). Patients with gynecologic cancer from low-income families faced a higher risk of catastrophic expenditures than those of higher icomes (24.4% vs 2.9%; P<.001). Among the patients from low-income families, Medicaid coverage was associated with a lower risk of catastrophic spending than private insurance. After the Affordable Care Act implementation, we observed reductions in the risk of uninsurance, but there was no significant change in the risk of catastrophic spending among patients with gynecologic cancer.

Conclusion Patients with gynecologic cancer faced high risks of uninsurance, nonemployment, and catastrophic health expenditures, particularly among patients from low-income families. Catastrophic spending was uncommon in the absence of either nonemployment or uninsurance in a given year.

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial.

MA Powell, VL Filiaci, ML Hensley, HQ Huang, KN Moore, KS Tewari, LJ Copeland, AA Secord, DG Mutch, A Santin, DP Warshal, NM Spirtos, PA DiSilvestro, OB Ioffe, DS Miller. Journal of Clinical Oncology 2022 40:9, 968-977. DOI: 10.1200/JCO.21.02050 https://ascopubs.org/doi/full/10.1200/JCO.21.02050

PURPOSE This phase III randomized trial (NCT00954174) tested the null hypothesis that paclitaxel and carboplatin (PC) is inferior to paclitaxel and ifosfamide (PI) for treating uterine carcinosarcoma (UCS).

PATIENTS AND METHODS Adults with chemotherapy-naïve UCS or ovarian carcinosarcoma (OCS) were randomly assigned to PC or PI with 3-week cycles for 6-10 cycles. With 264 events in patients with UCS, the power for an overall survival (OS) hybrid noninferiority design was 80% for a null hazard ratio (HR) of 1.2 against a 13% greater death rate on PI with a type I error of 5% for a one-tailed test.

RESULTS The study enrolled 536 patients with UCS and 101 patients with OCS, with 449 and 90 eligible, respectively. Primary analysis was on patients with UCS, distributed as follows: 40% stage I, 6% stage II, 31% stage III, 15% stage IV, and 8% recurrent. Among eligible patients with UCS, PC was assigned to 228 and PI to 221. PC was not inferior to PI. The median OS was 37 versus 29 months (HR = 0.87; 90% CI, 0.70 to 1.075; P < .01 for noninferiority, P > .1 for superiority). The median progression-free survival was 16 versus 12 months (HR = 0.73; P = < 0.01 for noninferiority, P < .01 for superiority). Toxicities were similar, except that more patients in the PC arm had hematologic toxicity and more patients in the PI arm had confusion and genitourinary hemorrhage. Among 90 eligible patients with OCS, those in the PC arm had longer OS (30 v 25 months) and progression-free survival (15 v 10 months) than those in the PI arm, but with limited precision, these differences were not statistically significant.

CONCLUSION PC was not inferior to the active regimen PI and should be standard treatment for UCS.

Dual PD-1 and CTLA-4 Checkpoint Blockade Using Balstilimab and Zalifrelimab Combination as Second-Line Treatment for Advanced Cervical Cancer: An Open-Label Phase II Study

David M. O'Malley, Maryna Neffa, Bradley J. Monk, Tamar Melkadze, Marilyn Huang, Anna Kryzhanivska, Iurie Bulat, Tarek M. Meniawy, Andrea Bagameri, Edward W. Wang, Bernard Doger de Speville Uribe, Roberto Hegg, Waldo Ortuzar Feliu, Marek Ancukiewicz, and Iwona Lugowska. Journal of Clinical Oncology 2022 40:7, 762-771 DOI: 10.1200/JCO.21.02067 https://ascopubs.org/doi/full/10.1200/JCO.21.02067

PURPOSE Balstilimab (antiprogrammed death-1) and zalifrelimab (anticytotoxic T-lymphocyte–associated antigen-4) are two new checkpoint inhibitors emerging as promising investigational agents for the treatment of advanced cervical cancer. This phase II trial (ClinicalTrials.gov identifier: NCT03495882) evaluated the combination of balstilimab plus zalifrelimab in patients with recurrent and/or metastatic cervical cancer who relapsed after prior platinum-based therapy.

PATIENTS AND METHODS Patients were intravenously dosed with balstilimab 3 mg/kg once every 2 weeks and zalifrelimab 1 mg/kg once every 6 weeks, for up to 24 months. The primary end point was objective response rate (ORR, RECIST version 1.1, assessed by independent central review). Secondary end points included duration of response, safety and tolerability, and survival.

RESULTS In total, 155 women (median age, 50 years [range, 24-76 years]) were enrolled and treated with balstilimab plus zalifrelimab; 125 patients had measurable disease at baseline and one prior line of platinum-based therapy in the advanced setting, and these patients constituted the efficacy-evaluable population. The median follow-up was 21 months. The confirmed ORR was 25.6% (95% CI, 18.8 to 33.9), including 10 complete responders and 22 partial responders, with median duration of response not reached (86.5%, 75.5%, and 64.2% at 6, 9, and 12 months, respectively). The ORRs were 32.8% and 9.1% in patients with programmed death ligand-1–positive and programmed death ligand-1–negative tumors, respectively. For patients with squamous cell carcinoma, the ORR was 32.6%. The overall disease control rate was 52% (95% CI, 43.3 to 60.6). Hypothyroidism (14.2%) and hyperthyroidism (7.1%) were the most common immune-mediated adverse events.

CONCLUSION Promising and durable clinical activity, with favorable tolerability, was seen in this largest trial to date evaluating dual programmed death-1/cytotoxic T-lymphocyte–associated antigen-4 blockade in patients with recurrent and/or metastatic cervical cancer. Further investigation of the balstilimab and zalifrelimab combination in this setting is continuing.

Pembrolizumab in Patients With Microsatellite Instability–High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study.

DM O'Malley, GM Bariani, PA Cassier, A Marabelle, AR Hansen, AD Acosta, WH Miller Jr, T Safra, A Italiano, L Mileshkin, L Xu, F Jin, K Norwood, M Maio. Journal of Clinical Oncology 2022 40:7, 752-761 DOI: 10.1200/JCO.21.01874 https://ascopubs.org/doi/full/10.1200/JCO.21.01874

PURPOSE Pembrolizumab demonstrated durable antitumor activity in patients with previously treated, advanced microsatellite instability–high or mismatch repair–deficient (MSI-H/dMMR) tumors, including endometrial cancer, in the nonrandomized, open-label, multicohort, phase II KEYNOTE-158 study (NCT02628067). We report efficacy and safety outcomes for patients with MSI-H/dMMR endometrial cancer enrolled in KEYNOTE-158.

METHODS Eligible patients from cohorts D (endometrial cancer, regardless of MSI-H/dMMR status) and K (any MSI-H/dMMR solid tumor, except colorectal) with previously treated, advanced MSI-H/dMMR endometrial cancer received pembrolizumab 200 mg once every 3 weeks for 35 cycles. The primary end point was objective response rate per RECIST version 1.1 by independent central radiologic review. Secondary end points included duration of response, progression-free survival, overall survival, and safety.

RESULTS As of October 5, 2020, 18 of 90 treated patients (20%) had completed 35 cycles of pembrolizumab and 52 (58%) had discontinued treatment. In the efficacy population (patients who received ≥ 1 dose of pembrolizumab and had ≥ 26 weeks of follow-up; N = 79), the median time from first dose to data cutoff was 42.6 (range, 6.4-56.1) months. The objective response rate was 48% (95% CI, 37 to 60), and median duration of response was not reached (2.9-49.7+ months). Median progression-free survival was 13.1 (95% CI, 4.3 to 34.4) months, and median overall survival was not reached (95% CI, 27.2 months to not reached). Among all treated patients, 76% had ≥ 1 treatment-related adverse event (grades 3-4, 12%). There were no fatal treatment-related events. Immune-mediated adverse events or infusion reactions occurred in 28% of patients (grades 3-4, 7%; no fatal events).

CONCLUSION Pembrolizumab demonstrated robust and durable antitumor activity and encouraging survival outcomes with manageable toxicity in patients with previously treated, advanced MSI-H/dMMR endometrial cancer.

A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability.

S Bellone, DM Roque, ER Siegel, N Buza, P Hui, E Bonazzoli, A Guglielmi, L Zammataro, N Nagarkatti, S Zaidi, J Lee, D-A Silasi, GS Huang, V Andikyan, S Damast, M Clark, M Azodi, PE Schwartz, JR Tymon-Rosario, JA Harold, D Mauricio, B Zeybek, G Menderes, G Altwerger, E Ratner, LB Alexandrov, A Iwasaki, Y Kong, E Song, W Dong, JA Elvin, J Choi, AD. Santin, *Cancer*. 128 (6) 1206-1218 2022. https://doi.org/10.1002/cncr.34025
https://acsjournals.onlinelibrary.wiley.com/action/showCitFormats?doi=10.1002%2Fcncr.34025

Background Microsatellite instability–high (MSI-H)/mismatch repair deficiency (dMMR) is a biomarker for responses to immune checkpoint inhibitors (ICIs). Whether mechanisms underlying microsatellite instability alter responses to ICIs is unclear. This article reports data from a prospective phase 2 pilot study of pembrolizumab in patients with recurrent MSI-H endometrial cancer (EC) analyzed by whole exome sequencing (WES) and potential mechanisms of primary/secondary ICI resistance (NCT02899793).
Methods Patients with measurable MSI-H/dMMR EC confirmed by polymerase chain reaction/immunohistochemistry were evaluated by WES and received 200 mg of pembrolizumab every 3 weeks for ≤2 years. The primary end point was the objective response rate (ORR). Secondary end points included progression-free survival (PFS) and overall survival (OS).
Results Twenty-five patients (24 evaluable) were treated. Six patients (25%) harbored Lynch/Lynch-like tumors, whereas 18 (75%) had sporadic EC. The tumor mutation burden was higher in Lynch-like tumors (median, 2939 mutations/megabase [Mut/Mb]; interquartile range [IQR], 867-5108 Mut/Mb) than sporadic tumors (median, 604 Mut/Mb; IQR, 411-798 Mut/Mb; *P* = .0076). The ORR was 100% in Lynch/Lynch-like patients but only 44% in sporadic patients (*P* = .024). The 3-year PFS and OS proportions were 100% versus 30% (*P* = .017) and 100% versus 43% (*P* = .043), respectively.
Conclusions This study suggests prognostic significance of Lynch-like cancers versus sporadic MSI-H/dMMR ECs for ORR, PFS, and OS when patients are treated with pembrolizumab. Larger confirmatory studies in ECs and other MSI-H/dMMR tumors are necessary. Defective antigen processing/presentation and deranged induction in interferon responses serve as mechanisms of resistance in sporadic MSI-H ECs. Oligoprogression in MSI-H/dMMR patients appears salvageable with surgical resection and/or local treatment and the continuation of pembrolizumab off study. Clinical studies evaluating separate MSI-H/dMMR EC subtypes treated with ICIs are warranted.

Prospective Cohort Study of Pre- and Postdiagnosis Obesity and Endometrial Cancer Survival.

RL Kokts-Porietis, J McNeil, AR Morielli, LS Cook, KS Courneya, CM Friedenreich, JNCI: Journal of the National Cancer Institute, Volume 114, (3) 2022, 409–418, https://doi.org/10.1093/jnci/djab197
https://academic.oup.com/jnci/article-abstract/114/3/409/6379716?redirectedFrom=fulltext
Background Disease-free survival (DFS) and overall survival (OS) associations with anthropometric measures of obesity and changes in these exposures remain unknown among endometrial cancer survivors.
Methods Endometrial cancer survivors diagnosed between 2002 and 2006 completed direct anthropometric measurements and self-reported lifetime weight history during in-person interviews approximately 4 months after diagnosis (peridiagnosis) and approximately 3 years after diagnosis (follow-up). Participants were followed-up until death or March 20, 2019. Cox proportional regression was used to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for body mass index (BMI), weight, waist circumference, and waist-hip ratio with DFS and OS. Statistical tests were 2-sided.
Results A total of 540 and 425 cancer survivors were assessed peridiagnosis and follow-up, respectively. During the median 14.2 years of follow-up (range = 0.3-16.5 years), 132 participants had a recurrence and/or died (DFS), with 111 deaths overall (OS). Reduced DFS was noted with greater recalled weight 1 year before diagnosis (HR = 1.88, 95% CI = 1.15 to 3.07), BMI 1 year before diagnosis (HR = 1.88, 95% CI = 1.09 to 3.22), and measured peridiagnosis BMI (HR = 2.04, 95% CI = 1.18 to 3.53). Measured peridiagnosis waist circumference of at least 88 cm was associated with decreased DFS (HR = 1.94, 95% CI = 1.24 to 3.03) and OS (HR = 1.90, 95% CI = 1.16 to 3.13). A twofold decrease in DFS and OS was associated with a BMI of at least 5% or weight change from 1 year before diagnosis to peridiagnosis. No associations were observed for the assessment during follow-up.
Conclusions One-year before- and peridiagnosis anthropometric measures of obesity were associated with reduced survival among endometrial cancer survivors. Anthropometric changes from 1 year before to peridiagnosis may provide an important indication of future survival in this population.

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. Utilizing 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, DM O'Malley, O Dorigo, S Gaillard, H Gabra, B Slomovitz, P 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).