Ed's List
January 2022

In The Know

Gyn Onc Literature of Significance

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

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

January

Ovarian Cancer Is Not So Silent, Goff, BA Obstetrics & Gynecology: 2022 - 139 – (2) - p 155-156 doi: 10.1097/AOG.0000000000004664
https://journals.lww.com/greenjournal/Fulltext/2022/02000/Ovarian_Cancer_Is_Not_So_Silent.1.aspx
One of the concerns about the symptoms of ovarian cancer is that they can be vague and commonly present in the general population. In a case–control study of more than 1,600 women presenting to a primary care clinic compared with women with early-stage ovarian cancer, the odds ratios for symptoms were 2.2 for abdominal or pelvic pain, 2.4 for urinary urgency, 2.5 for difficulty eating, 3.6 for bloating, and 7.4 for increased abdominal size. However, the more significant findings were that women with ovarian cancer typically had symptoms that were of more recent onset and experienced their symptoms almost daily, compared with over a year-long history of episodic symptoms occurring two to three times a month for the clinic population. Chan et al were not able to assess for frequency or duration of symptoms, which may be an important factor in distinguishing symptoms that are more concerning for ovarian cancer. Other researchers have developed an ovarian cancer symptom index, which includes having one of six symptoms (abdominal or pelvic pain, increased abdominal size or bloating, and difficulty eating or feeling full quickly), with these symptoms occurring more than 12 times a month and being present for less than a year as being moderately sensitive (67–87%), with specificity of 80–90% in women with ovarian cancer. Symptom-triggered screening has been used successfully in prospective studies. In the DOvE trial (Diagnosing Ovarian Cancer Early), investigators found that assessment of ovarian cancer symptoms followed by diagnostic testing with pelvic ultrasonography and CA 125 led to a high detection rate and a trend toward earlier diagnosis and better outcomes.[10] Importantly, the incidence of ovarian cancer in the symptomatic population was more than 10 times greater than in the general public.
The study by Chan et al adds more information that a large majority of women with ovarian cancer, even those with early-stage disease, have symptoms. Both patients and health care professionals should be educated about these symptoms, and we all need a high index of suspicion in symptomatic patients to avoid delays in diagnosis. Women with early-stage disease have survival rates that are more than double those in women with advanced-stage disease; therefore, symptom recognition with appropriate diagnostic testing remains very important in our efforts to improve outcomes.

Symptoms of Women With High-Risk Early-Stage Ovarian Cancer. Chan, JK, C Tian, K Chunqiao, KP Kesterson, BJ Monk, DS Kapp, B Davidson, S Robertson, LJ Copeland, JL Walker, RM Wenham, Y Casablanca, NM Spirtos, KS Tewari, JG Bell. Obstetrics & Gynecology: 2022 - 139 – (2) - p 157-162 doi: 10.1097/AOG.0000000000004642
https://journals.lww.com/greenjournal/Fulltext/2022/02000/Symptoms_of_Women_With_High_Risk_Early_Stage.2.aspx
OBJECTIVE: To assess the presentation, characteristics, and prognostic significance of symptoms in patients with high-risk early-stage epithelial ovarian cancer.
METHODS: A retrospective chart review was performed on all patients enrolled in a phase III clinical trial (GOG 157). All patients had surgically staged, high-risk early-stage epithelial ovarian cancer (stage IA–IB and grade 3, any clear cell, stage IC or II). Chi-square and Kaplan-Meier estimates and Cox proportional hazards models were used for statistical analyses.
RESULTS: Of 419 patients evaluated for symptoms, 301 (72%) presented with one or more symptoms, and 118 (28%) were asymptomatic but had a mass found on examination. Forty percent had only one symptom, and 32% had more than one symptom. Among those with at least one symptom, the most common were abdominal and pelvic pain (31%), and increased girth or fullness (26%). Overall, 23% of patients with tumors 10 cm or smaller, 27% of patients with tumors larger than 10 cm to 15 cm, and 46% of patients with tumors larger than 15 cm had multiple symptoms (*P*<.001). There was no

significant difference in presentation of symptoms based on age, stage, or histologic subtype. Symptoms at diagnosis were not associated with recurrence or survival.

CONCLUSION: More than 70% of patients with high-risk early-stage, epithelial ovarian cancer present with one or more symptoms, with the most common being abdominal or pelvic pain. The proportion of women with symptoms and the number of symptoms increase with enlarging tumor size.

Use of Germline *BRCA* Testing in Patients With Ovarian Cancer and Commercial Insurance. Cham S, Landrum MB, Keating NL, Armstrong J, Wright AA. *JAMA Netw Open.* 2022;5(1):e2142703. doi:10.1001/jamanetworkopen.2021.42703

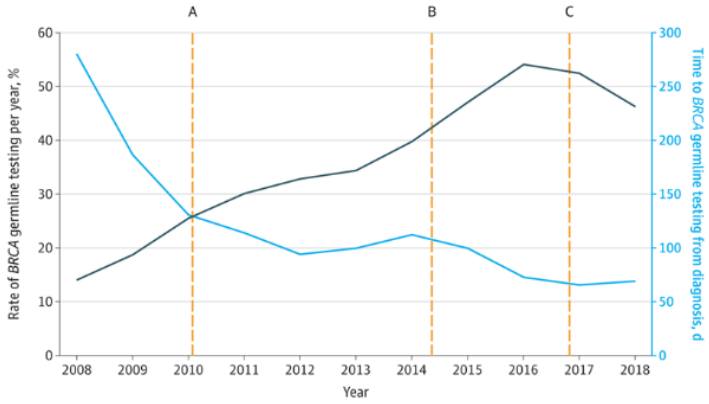
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787937?guestAccessKey=39bfec12-1483-4897-9912-3be654a0186e&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Introduction Approximately 15% of patients with ovarian cancer have a germline *BRCA* (g*BRCA)* variation, which has important implications, including increased sensitivity to platinum-based chemotherapy and poly(ADP-ribose) polymerase inhibitors and improved survival. Testing first-degree relatives is also cost-effective cancer prevention. Since 2010, guidelines have recommended universal testing in ovarian cancer. However, testing rates are reportedly between 10% and 30%, and few studies have examined commercially insured populations or identified patient-, physician-, and practice-level characteristics associated with testing rates.

Methods Using data from a large national commercial insurer, this cross-sectional study included 12 989 patients with claims for ovarian, fallopian, or primary peritoneal cancers and a biopsy or surgery between 2008 and 2018. We restricted the cohort to patients with a biopsy or surgery and carboplatin or cisplatin within 6 months. We excluded those without surgery or outpatient visits, with less than 12 months of continuous insurance, with missing zip codes, or who were younger than 18 years (eFigure in the Supplement). We attributed patients to practices and physicians using outpatient evaluation and management claims with a diagnosis 6 months or less from the first outpatient claim for chemotherapy (eAppendix in the Supplement). The Harvard Medical School Committee on Human Studies deemed the study exempt from review and the requirement for informed consent because the study was a secondary analysis of previously collected data. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

The primary outcome was *gBRCA* testing using gene-specific and methodology-based procedure codes (eTable in the Supplement). Secondary outcomes included timeliness (ie, ≤6 months from biopsy/surgery) and median time from first chemotherapy claim to testing. We used χ^2 tests and linear regression to assess patient, physician, and practice characteristics associated with outcomes. A 2-sided $P \leq .05$ was considered statistically significant. Analyses were performed using SAS statistical software version 14.1 (SAS Institute).

Results Among 3603 women with ovarian cancer (mean [SD] age, 57.0 [11.3] years), 1220 (33.9%) received g*BRCA* testing (Table). Testing rates increased from 14.7% (55 of 375 patients) in 2008 to 46.4% (96 of 207 patients) in 2018; the median time to testing decreased from 280.0 to 72.5 days (Figure). In adjusted analyses, testing was lower for older women (women ≥65 years vs <50 years: adjusted difference, −20.8 percentage points; 95% CI, −25.8 to −16.4 percentage points) and women with more comorbidities (Charlson Comorbidity Index score ≥2 vs 0: adjusted difference, −4.6 percentage points; 95% CI, −8.9 to −0.2 percentage points). Testing rates were similar among oncologists (medical vs gynecologic oncologist: adjusted difference, 1.5 percentage points; 95% CI, −1.8 to 4.7 percentage points) and lower in other physicians (other vs gynecologic oncologist: adjusted difference, −5.9 percentage points; 95% CI, −10.3 to −1.5 percentage points). Testing was higher at academic and NCI cancer centers compared with community practices (academic vs NCI: adjusted difference, 0.5 percentage points; 95% CI, −7.2 to 8.4 percentage points; community vs NCI: adjusted difference, −4.5 percentage points; 95% CI, −8.8 to −0.2 percentage points]). There was a statistically significant increase in testing over time (2018 vs 2008: adjusted difference, 32.0 percentage points; 95% CI, 24.4-39.7 percentage points), although rates remained below 50% for most years (Table). Results were similar for analyses of timeliness of *gBRCA* testing, which significantly improved from 2010 to 2018 (Table).



Discussion Despite unequivocal recommendations for universal genetic testing in ovarian cancer, only 33.9% of patients with commercial insurance were tested between 2008 and 2018—clear evidence it remains underused—and a minority received timely testing. In this study, medical and gynecologic oncologists had similar rates of testing, while other physicians tested less often, perhaps reflecting a lack of knowledge of guidelines. Nearly 80% of patients received care in community practices, where rates were statistically lower. Although independent practices often lack access to genetic counselors, women in this study had insurance coverage for in-person and telephonic counseling. Future studies should examine barriers to timely testing to identify scalable strategies for increasing

testing, particularly for older women in community practices. Interventions targeting clinicians are essential because the absence of physician recommendations remains the largest barrier to testing.[6] Study limitations include the use of biopsy/surgery for diagnosis date, limited sociodemographic characteristics, and the possibility that women received testing later.

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, Fujiwara K, Pignata S, Baron-Hay S, Ray-Coquard I, Shapira-Frommer R, Ushijima K, Sakata J, Yonemori K, Kim YM, Guerra EM, Sanli UA, McCormack MM, Smith AD, Keefe S, Bird S, Dutta L, Orlowski RJ, Lorusso D; Study 309–KEYNOTE-775 Investigators. N Engl J Med. 2022 Jan 19. doi: 10.1056/NEJMoa2108330.
https://www.nejm.org/doi/full/10.1056/NEJMoa2108330?query=TOC&cid=NEJM+eToc%2C+January+20%2C+2022+DM641104_NEJM_Non_Subscriber&bid=789231360

BACKGROUND Standard therapy for advanced endometrial cancer after failure of platinum-based chemotherapy remains unclear.

METHODS In this phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with advanced endometrial cancer who had previously received at least one platinum-based chemotherapy regimen to receive either lenvatinib (20 mg, administered orally once daily) plus pembrolizumab (200 mg, administered intravenously every 3 weeks) or chemotherapy of the treating physician's choice (doxorubicin at 60 mg per square meter of body-surface area, administered intravenously every 3 weeks, or paclitaxel at 80 mg per square meter, administered intravenously weekly [with a cycle of 3 weeks on and 1 week off]). The two primary end points were progression-free survival as assessed on blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and overall survival. The end points were evaluated in patients with mismatch repair–proficient (pMMR) disease and in all patients. Safety was also assessed.

RESULTS A total of 827 patients (697 with pMMR disease and 130 with mismatch repair–deficient disease) were randomly assigned to receive lenvatinib plus pembrolizumab (411 patients) or chemotherapy (416 patients). The median progression-free survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 6.6 vs. 3.8 months; hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.50 to 0.72; P<0.001; overall: 7.2 vs. 3.8 months; hazard ratio, 0.56; 95% CI, 0.47 to 0.66; P<0.001). The median overall survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 17.4 vs. 12.0 months; hazard ratio for death, 0.68; 95% CI, 0.56 to 0.84; P<0.001; overall: 18.3 vs. 11.4 months; hazard ratio, 0.62; 95% CI, 0.51 to 0.75; P<0.001). Adverse events of grade 3 or higher occurred in 88.9% of the patients who received lenvatinib plus pembrolizumab and in 72.7% of those who received chemotherapy.

CONCLUSIONS Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer.

Reproductive factors do not influence survival with ovarian cancer. MT Phung, A Alimujiang, A Berchuck, H Anton-Cluver, JM Schildkraut, EV Bandera, J Chang-Claude, A Chase, JA Doherty, B Grout, MT Goodman, GE Hanley, AW Lee, CM Deurloo, U Menon, F Modugno, PDP Pharoah, MC Pike, J Richardson, HA Risch, W Sieh, KL Terry, PM Webb, N Wentzensen, AH Wu, CL Pearce. Cancer Epidemiol Biomarkers Prev January 21 2022 DOI: 10.1158/1055-9965.EPI-21-1091 https://cebp.aacrjournals.org/content/early/2022/01/21/1055-9965.EPI-21-1091.full-text.pdf

Background Previous studies on the association between reproductive factors and ovarian cancer survival are equivocal, possibly due to small sample sizes.

Methods Using data on 11,175 people diagnosed with primary invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer (ovarian cancer) from 16 studies in the Ovarian Cancer Association Consortium (OCAC), we examined the associations between survival and age at menarche, combined oral contraceptive use, parity, breastfeeding, age at last pregnancy, and menopausal status using Cox proportional hazard models. The models were adjusted for age at diagnosis, race/ethnicity, education level, and OCAC study and stratified on stage and histotype.

Results During the mean follow-up of 6.34 years (SD=4.80), 6,418 patients passed away (57.4%). There was no evidence of associations between the reproductive factors and survival among ovarian cancer patients overall or by histotype.

Conclusions This study found no association between reproductive factors and survival after an ovarian cancer diagnosis. Impact Reproductive factors are well-established risk factors for ovarian cancer, but they are not associated with survival after a diagnosis of ovarian cancer.

Improving the quality of care for patients with advanced epithelial ovarian cancer: Program components, implementation barriers, and recommendations. Temkin, SM, Smeltzer, MP, Dawkins, MD, Boehmer, LM, Senter, L, Black, DR, Blank, SV, Yemelyanova, A, Magliocco, AM, Finkel, MA, Moore, TE, Thaker, PH. Cancer. 2022. https://doi.org/10.1002/cncr.34023
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.34023?campaign=woletoc

The high lethality of ovarian cancer in the United States and associated complexities of the patient journey across the cancer care continuum warrant an assessment of current practices and barriers to quality care in the United States. The objectives of this study were to identify and assess key components in the provision of high-quality care delivery for patients with ovarian cancer, identify challenges in the implementation of best practices, and develop corresponding quality-related recommendations to guide multidisciplinary ovarian cancer programs and practices. This multiphase ovarian cancer quality-care initiative was guided by a multidisciplinary expert steering committee, including gynecologic oncologists, pathologists, a genetic counselor, a nurse navigator, social workers, and cancer center administrators. Key partnerships were also established. A collaborative approach was adopted to develop comprehensive recommendations by identifying ideal quality-of-care program components in advanced epithelial ovarian cancer management. The core program components included: care coordination and patient education, prevention and screening, diagnosis and initial management, treatment planning, disease surveillance, equity in care, and quality of life. Quality-directed recommendations were developed across 7 core program components, with a focus on ensuring high-quality ovarian cancer care delivery for patients through improved patient education and engagement by addressing unmet medical and supportive care needs. Implementation challenges were described, and key recommendations to overcome barriers were provided. The recommendations emerging from this initiative can serve as a comprehensive resource guide for multidisciplinary cancer practices, providers, and other stakeholders working to provide quality-directed cancer care for patients diagnosed with ovarian cancer and their families.

Global Burden of Disease 2019 Cancer Collaboration. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *JAMA Oncol.* Published online December 30, 2021. doi:10.1001/jamaoncol.2021.6987
https://jamanetwork.com/journals/jamaoncology/fullarticle/2787350?guestAccessKey=7b0fe21a-04b6-4f0b-bb93-fcc01eb5a6df&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamaoncology&utm_term=mostread&utm_content=olf-widget_01272022

Key Points

Question What was the burden of cancer globally and across Sociodemographic Index (SDI) groupings in 2019, and how has incidence, morbidity, and mortality changed since 2010?

Findings In this systematic analysis, there were 23.6 million new global cancer cases in 2019 (17.2 million when excluding those with nonmelanoma skin cancer), 10.0 million cancer deaths, and an estimated 250 million disability-adjusted life years estimated to be due to cancer; since 2010, these represent increases of 26.3%, 20.9%, and 16.0%, respectively. Absolute cancer burden increased in all SDI quintiles since 2010, but the largest percentage increases occurred in the low and low-middle SDI quintiles.

Meanings The study results suggest that increased cancer prevention and control efforts are needed to equitably address the evolving and increasing burden of cancer across the SDI spectrum.

Abstract

Importance The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019) provided systematic estimates of incidence, morbidity, and mortality to inform local and international efforts toward reducing cancer burden.

Objective To estimate cancer burden and trends globally for 204 countries and territories and by Sociodemographic Index (SDI) quintiles from 2010 to 2019.

Evidence Review The GBD 2019 estimation methods were used to describe cancer incidence, mortality, years lived with disability, years of life lost, and disability-adjusted life years (DALYs) in 2019 and over the past decade. Estimates are also provided by quintiles of the SDI, a composite measure of educational attainment, income per capita, and total fertility rate for those younger than 25 years. Estimates include 95% uncertainty intervals (UIs).

Findings In 2019, there were an estimated 23.6 million (95% UI, 22.2-24.9 million) new cancer cases (17.2 million when excluding nonmelanoma skin cancer) and 10.0 million (95% UI, 9.36-10.6 million) cancer deaths globally, with an estimated 250 million (235-264 million) DALYs due to cancer. Since 2010, these represented a 26.3% (95% UI, 20.3%-32.3%) increase in new cases, a 20.9% (95% UI, 14.2%-27.6%) increase in deaths, and a 16.0% (95% UI, 9.3%-22.8%) increase in DALYs. Among 22 groups of diseases and injuries in the GBD 2019 study, cancer was second only to cardiovascular diseases for the number of deaths, years of life lost, and DALYs globally in 2019. Cancer burden differed across SDI quintiles. The proportion of years lived with disability that contributed to DALYs increased with SDI, ranging from 1.4% (1.1%-1.8%) in the low SDI quintile to 5.7% (4.2%-7.1%) in the high SDI quintile. While the high SDI quintile had the highest number of new cases in 2019, the middle SDI quintile had the highest number of cancer deaths and DALYs. From 2010 to 2019, the largest percentage increase in the numbers of cases and deaths occurred in the low and low-middle SDI quintiles.

Conclusions and Relevance The results of this systematic analysis suggest that the global burden of cancer is substantial and growing, with burden differing by SDI. These results provide comprehensive and comparable estimates that can potentially inform efforts toward equitable cancer control around the world.

European cancer mortality predictions for the year 2022 with focus on ovarian cancer. M. Dalmartello, C. La Vecchia, P. Bertuccio, P. Boffetta, F. Levi, E. Negri, M. Malvezzi. Annals of Oncology 2022 https://doi.org/10.1016/j.annonc.2021.12.007. https://www.sciencedirect.com/science/article/pii/S092375342104881X

Background Cancer mortality rates, though not absolute numbers of deaths, have been decreasing over the last three decades in Europe.

Materials and methods We estimated projections and the number of avoided deaths for total cancer mortality and 10 major cancer sites, between 1989 and 2022, for the European Union (EU), the UK, France, Germany, Italy, Poland and Spain using cancer death certification and population data since 1970 from the World Health Organization and Eurostat.

Results In the EU, we predict 1 269 200 cancer deaths in 2022; corresponding age-standardized rates (world) fall 6% to 126.9 deaths/100 000 in men and 4% to 80.2/100 000 women since 2017. Male lung cancer is expected to fall 10% reaching 30.9/100 000. The rise in female lung cancer mortality slowed (+2% to 13.8/100 000). We estimated 369 000 (23%) avoided deaths in 2022 alone and a total of 5 394 000 (12%) deaths since the peak rate in 1988. Stomach, colorectal, breast and prostate cancers showed substantial declines, between 5% and 16% over the past 5 years. Pancreatic cancer remained stable in men (8.1/100 000) and rose 3% in women (5.9/100 000), becoming the third cause of cancer mortality in the EU (87 300 deaths), overtaking breast cancer (86 300 deaths). The fall in uterine cancers slowed down (−4%) to 4.7/100 000. Bladder cancer fell 9% in men, but was stable in women. Leukaemias fell more than 10%. Ovarian cancer mortality declined over the past decade in all considered countries. EU predicted rates were 4.3/100 000 (−13%) all ages, 1.2/100 000 (−26%) at 20-49, 15.3/100 000 (−11%) at 50-69 and 32.3/100 000 (−11%) at 70-79 years.

Conclusions We predicted additional declines in cancer mortality rates for 2022. The slowdown in female lung cancer mortality reflects some levelling of smoking in women. Favourable ovarian cancer trends are likely to continue and are largely attributable to the spreading oral contraceptive use and some impact of improved diagnosis and management.

Assessment of US Preventive Services Task Force Guideline–Concordant Cervical Cancer Screening Rates and Reasons for Underscreening by Age, Race and Ethnicity, Sexual Orientation, Rurality, and Insurance, 2005 to 2019. Suk R, Hong Y, Rajan SS, Xie Z, Zhu Y, Spencer JC. *JAMA Netw Open.* 2022;5(1):e2143582. doi:10.1001/jamanetworkopen.2021.43582

Key Points

Question What proportion of screening-eligible women do not have up-to-date US Preventive Services Task Force guideline–concordant cervical cancer screening status, and what are their primary reasons for not receiving timely screening?

Findings In this cross-sectional study of 20 557 women (weighted, 113 million women) eligible for cervical cancer screening in the US, the proportion of women without up-to-date screening significantly increased from 14.4% in 2005 to 23.0% in 2019 among all sociodemographic groups, with disparities found across different sociodemographic groups and lack of knowledge reported as the biggest barrier to receiving screening.

Meaning This study found that guideline-concordant cervical cancer screening rates decreased between 2005 and 2019; campaigns addressing patient knowledge and practitioner communication may help to improve cervical cancer screening rates, and cultural adaptation of interventions is needed to reduce existing disparities.

Abstract

Importance Cervical cancer screening rates are suboptimal in the US. Population-based assessment of reasons for not receiving screening is needed, particularly among women from historically underserved demographic groups.

Objective To estimate changes in US Preventive Service Task Force guideline–concordant cervical cancer screening over time and assess the reasons women do not receive up-to-date screening by sociodemographic factors.

Design, Setting, and Participants This pooled population-based cross-sectional study used data from the US National Health Interview Survey from 2005 and 2019. A total of 20 557 women (weighted, 113.1 million women) aged 21 to 65 years without previous hysterectomy were included. Analyses were conducted from March 30 to August 19, 2021.

Exposures Sociodemographic factors, including age, race and ethnicity, sexual orientation, rurality of residence, and health insurance type.

Main Outcomes and Measures Primary outcomes were US Preventive Services Task Force guideline–concordant cervical cancer screening rates and self-reported primary reasons for not receiving up-to-date screening. For 2005, up-to-date screening was defined as screening every 3 years for women aged 21 to 65 years. For 2019, up-to-date screening was defined as screening every 3 years with a Papanicolaou test alone for women aged 21 to 29 years and screening every 3 years with a Papanicolaou test alone or every 5 years with high-risk human papillomavirus testing or cotesting for women aged 30 to 65 years. Population estimation included sampling weights.

Results Among 20 557 women (weighted, 113.1 million women) included in the study, most were aged 30 to 65 years (16 219 women; weighted, 86.3 million women [76.3%]) and had private insurance (13 571 women; weighted, 75.8 million women [67.0%]). With regard to race and ethnicity, 997 women (weighted, 6.9 million women [6.1%]) were Asian, 3821 women (weighted, 19.5 million women [17.2%]) were Hispanic, 2862 women (weighted, 14.8 million women [13.1%]) were non-Hispanic Black, 12 423 women (weighted, 69.0 million women [61.0%]) were non-Hispanic White, and 453 women (weighted, 3.0 million women [2.7%]) were of other races and/or ethnicities (including Alaska Native and American Indian

[weighted, 955 000 women (0.8%)] and other single and multiple races or ethnicities [weighted, 2.0 million women (1.8%)]). In 2019, women aged 21 to 29 years had a significantly higher rate of overdue screening (29.1%) vs women aged 30 to 65 years (21.1%; *P* < .001). In both age groups, the proportion of women without up-to-date screening increased significantly from 2005 to 2019 (from 14.4% to 23.0%; *P* < .001). Significantly higher rates of overdue screening were found among those of Asian vs non-Hispanic White race and ethnicity (31.4% vs 20.1%; *P* = .01), those identifying as LGBQ+ (gender identity was not assessed because of a small sample) vs heterosexual (32.0% vs 22.2%; *P* < .001), those living in rural vs urban areas (26.2% vs 22.6%; *P* = .04), and those without insurance vs those with private insurance (41.7% vs 18.1%; *P* < .001). The most common reason for not receiving timely screening across all groups was lack of knowledge, ranging from 47.2% of women identifying as LGBQ+ to 64.4% of women with Hispanic ethnicity. Previous receipt of a human papillomavirus vaccine was not a primary reason for not having up-to-date screening (<1% of responses). From 2005 to 2019, among women aged 30 to 65 years, lack of access decreased significantly as a primary reason for not receiving screening (from 21.8% to 9.7%), whereas lack of knowledge (from 45.2% to 54.8%) and not receiving recommendations from health care professionals (from 5.9% to 12.0%) increased significantly.

Conclusions and Relevance This cross-sectional study found that cervical cancer screening that was concordant with US Preventive Services Task Force guidelines decreased in the US between 2005 and 2019, with lack of knowledge reported as the biggest barrier to receiving timely screening. Campaigns addressing patient knowledge and provider communication may help to improve screening rates, and cultural adaptation of interventions is needed to reduce existing disparities.

Targeting Fc Receptor-Mediated Effects and the "Don't Eat Me" Signal with an Oncolytic Virus Expressing an Anti-CD47 Antibody to Treat Metastatic Ovarian Cancer.

L Tian, B Xu, K- Teng, M Song, Z Zhu, Y Chen, J Wang, J Zhang, M Feng, B Kaur, L Rodriguez, MA Caligiuri, J Yu. Clin Cancer Res January 1 2022 (28) (1) 201-214; DOI: 10.1158/1078-0432.CCR-21-1248 https://clincancerres.aacrjournals.org/content/28/1/201

Purpose: mAbs blocking immune checkpoints have emerged as important cancer therapeutics, as exemplified by systemic administration of the IgG1 anti-CD47 mAb that blocks the "don't eat me" pathway. However, this strategy is associated with severe toxicity.

Experimental Design: To improve therapeutic efficacy while reducing toxicities for ovarian cancer, we engineered an oncolytic herpesvirus (oHSV) to express a full-length, soluble anti-CD47 mAb with a human IgG1 scaffold (OV-αCD47-G1) or IgG4 scaffold (OV-αCD47-G4).

Results: Both IgG1 and IgG4 anti-CD47 mAbs secreted by oHSV-infected tumor cells blocked the CD47–SIRPα signal pathway, enhancing macrophage phagocytosis against ovarian tumor cells. OV-αCD47-G1, but not OV-αCD47-G4, activated human NK-cell cytotoxicity and macrophage phagocytosis by binding to the Fc receptors of these cells. *In vivo*, these multifaceted functions of OV-αCD47-G1 improved mouse survival in xenograft and immunocompetent mouse models of ovarian cancer when compared with OV-αCD47-G4 and a parental oHSV. The murine counterpart of OV-αCD47-G1, OV-αmCD47-G2b, also enhanced mouse NK-cell cytotoxicity and macrophage phagocytosis and prolonged survival of mice bearing ovarian tumors compared with OV-αmCD47-G3. OV-αmCD47-G2b was also superior to αmCD47-G2b and showed a significantly better effect when combined with an antibody against PD-L1 that was upregulated by oHSV infection.

Conclusions: Our data demonstrate that an oHSV encoding a full-length human IgG1 anti-CD47 mAb, when used as a single agent or combined with another agent, is a promising approach for improving ovarian cancer treatment via enhancing innate immunity, as well as performing its known oncolytic function and modulation of immune cells.

Adavosertib with Chemotherapy in Patients with Primary Platinum-Resistant Ovarian, Fallopian Tube, or Peritoneal Cancer: An Open-Label, Four-Arm, Phase II Study.

KN Moore, SK Chambers, EP Hamilton, L Chen, AM Oza, SA Ghamande, GE Konecny, SC Plaxe, DL Spitz, JJJ Geenen, TA Troso-Sandoval, JM Cragun, E Imedio, S Kumar, GM Mugundu, Z Lai, J Chmielecki, SF Jones, DR Spigel, KA Cadoo Clin Cancer Res January 1 2022 (28) (1) 36-44; DOI: 10.1158/1078-0432.CCR-21-0158 https://clincancerres.aacrjournals.org/content/28/1/36

Purpose: This study assessed the efficacy, safety, and pharmacokinetics of adavosertib in combination with four chemotherapy agents commonly used in patients with primary platinum-resistant ovarian cancer.

Patients and Methods: Women with histologically or cytologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer with measurable disease were enrolled between January 2015 and January 2018 in this open-label, four-arm, multicenter, phase II study. Patients received adavosertib (oral capsules, 2 days on/5 days off or 3 days on/4 days off) in six cohorts from 175 mg once daily to 225 mg twice daily combined with gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin. The primary outcome measurement was overall response rate.

Results: Three percent of patients (3/94) had confirmed complete response and 29% (27/94) had confirmed partial response. The response rate was highest with carboplatin plus weekly adavosertib, at 66.7%, with 100% disease control rate, and median progression-free survival of 12.0 months. The longest median duration of response was in the paclitaxel cohort (12.0 months). The most common grade ≥3 adverse events across all cohorts were neutropenia [45/94 (47.9%) patients], anemia [31/94 (33.0%)], thrombocytopenia [30/94 (31.9%)], and diarrhea and vomiting [10/94 (10.6%) each].

Conclusions: Adavosertib showed preliminary efficacy when combined with chemotherapy. The most promising treatment combination was adavosertib 225 mg twice daily on days 1–3, 8–10, and 15–17 plus carboplatin every 21 days. However, hematologic toxicity was more frequent than would be expected for carboplatin monotherapy, and the combination requires further study to optimize the dose, schedule, and supportive medications.

Effect of Mismatch Repair Status on Outcome of Early-Stage Grade 1 to 2 Endometrial Cancer Treated With Vaginal Brachytherapy. AL Russo, LJ Lee, JY Wo, A Niemierko, D Park, G Alban, M King, L Philp, WB Growdon, E Oliva, DR Spriggs, OO Yeku., American Journal of Clinical Oncology: January 2022 - Volume 45 - Issue 1 - p 36-39 doi: 10.1097/COC.0000000000000871 https://journals.lww.com/amjclinicaloncology/Fulltext/2022/01000/Effect_of_Mismatch_Repair_Status_on_Outcome_of.6.aspx

Objectives: The objective of this study was to determine if deficiency of mismatch repair (dMMR) proteins in patients with early-stage favorable endometrial cancer treated with vaginal brachytherapy (VB) is associated with increased recurrence.

Materials and Methods: A multi-institutional retrospective cohort study of 141 patients with stage I to II grade 1 and 2 endometrioid adenocarcinoma treated with surgery and adjuvant VB was performed to compare recurrence risk in dMMR (n=41) versus MMR-preserved (pMMR) (n=100). Additional clinical and pathologic risk factors were also collected. Univariate analysis and multivariable analysis Cox regression analysis was performed to identify factors associated with any recurrence. Kaplan-Meier method and log rank test were used to compare recurrence free survival and overall survival (OS).

Results: Median follow up was 42 months. Forty-one patients (29%) were dMMR. There were 7 recurrences (17%) in dMMR versus 4 recurrences (4%) in pMMR (*P*=0.009). On univariate analysis of any recurrence, both dMMR (hazard ratio: 5.3, *P*=0.008) and stage (hazard ratio: 3.8, *P*=0.05) were statistically significantly associated with time to first recurrence. The 5-year recurrence free survival was 90% (95% CI: 73%-96%) in pMMR versus 61.0% (95% CI: 19%-86%) in dMMR (*P*=0.003). Five-year OS was 96% (95% CI: 76%-99%) in pMMR versus 86% (95% CI: 62%-95%) in dMMR (*P*=0.03).

Conclusions: MMR deficiency in stage I to II grade 1 to 2 endometrial cancer patients treated with adjuvant VB alone was associated with statistically significant increased risk for any recurrence and worse OS. MMR status may be an important prognosticator in this cohort of patients warranting adjuvant treatment intensification in the clinical trial setting.

Repurposing Ceritinib Induces DNA Damage and Enhances PARP Inhibitor Responses in High-Grade Serous Ovarian Carcinoma. A Kanakkanthara, X Hou, TL Ekstrom, V Zanfagnin, AM Huehls, RL Kelly, H Ding, MC Larson, G Vasmatzis, AL Oberg, SH Kaufmann, AS Mansfield, SJ Weroha, LM Karnitz. Cancer Res 2022 (82) (2) 307-319; DOI: 10.1158/0008-5472.CAN-21-0732 https://cancerres.aacrjournals.org/content/82/2/307

PARP inhibitors (PARPi) have activity in homologous recombination (HR) repair-deficient, high-grade serous ovarian cancers (HGSOC). However, even responsive tumors develop PARPi resistance, highlighting the need to delay or prevent the appearance of PARPi resistance. Here, we showed that the ALK kinase inhibitor ceritinib synergizes with PARPis by inhibiting complex I of the mitochondrial electron transport chain, which increases production of reactive oxygen species (ROS) and subsequent induction of oxidative DNA damage that is repaired in a PARP-dependent manner. In addition, combined treatment with ceritinib and PARPi synergized in HGSOC cell lines irrespective of HR status, and a combination of ceritinib with the PARPi olaparib induced tumor regression more effectively than olaparib alone in HGSOC patient-derived xenograft (PDX) models. Notably, the ceritinib and olaparib combination was most effective in PDX models with preexisting PARPi sensitivity and was well tolerated. These findings unveil suppression of mitochondrial respiration, accumulation of ROS, and subsequent induction of DNA damage as novel effects of ceritinib. They also suggest that the ceritinib and PARPi combination warrants further investigation as a means to enhance PARPi activity in HGSOC, particularly in tumors with preexisting HR defects.

Significance: The kinase inhibitor ceritinib synergizes with PARPi to induce tumor regression in ovarian cancer models, suggesting that ceritinib combined with PARPi may be an effective strategy for treating ovarian cancer.

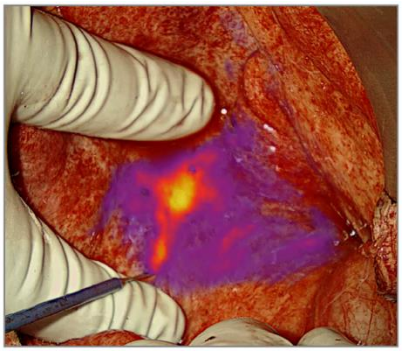
Neoadjuvant Chemotherapy Induces Genomic and Transcriptomic Changes in Ovarian Cancer. M Javellana, MA Eckert, J Heide, K Zawieracz, M Weigert, S Ashley, E Stock, D Chapel, L Huang, SD Yamada, AA Ahmed, RR Lastra, M Chen, E Lengyel. Cancer Res 2022 (82) (1) 169-176; DOI: 10.1158/0008-5472.CAN-21-1467 https://cancerres.aacrjournals.org/content/82/1/169

The growing use of neoadjuvant chemotherapy to treat advanced stage high-grade serous ovarian cancer (HGSOC) creates an opportunity to better understand chemotherapy-induced mutational and gene expression changes. Here we performed a cohort study including 34 patients with advanced stage IIIC or IV HGSOC to assess changes in the tumor genome and transcriptome in women receiving neoadjuvant chemotherapy. RNA sequencing and panel DNA sequencing of 596 cancer-related genes was performed on paired formalin-fixed paraffin-embedded specimens collected before and after chemotherapy, and differentially expressed genes (DEG) and copy-number variations (CNV) in pre- and post-chemotherapy samples were identified. Following tissue and sequencing quality control, the final patient cohort consisted of 32 paired DNA and 20 paired RNA samples. Genomic analysis of paired samples did not reveal any recurrent chemotherapy-induced

mutations. Gene expression analyses found that most DEGs were upregulated by chemotherapy, primarily in the chemotherapy-resistant specimens. AP-1 transcription factor family genes (*FOS*, *FOSB*, *FRA-1*) were particularly upregulated in chemotherapy-resistant samples. CNV analysis identified recurrent 11q23.1 amplification, which encompasses *SIK2*. *In vitro*, combined treatment with AP-1 or SIK2 inhibitors with carboplatin or paclitaxel demonstrated synergistic effects. These data suggest that AP-1 activity and *SIK2* copy-number amplification are induced by chemotherapy and may represent mechanisms by which chemotherapy resistance evolves in HGSOC. AP-1 and SIK2 are druggable targets with available small molecule inhibitors and represent potential targets to circumvent chemotherapy resistance.
Significance: Genomic and transcriptomic analyses identify increased AP-1 activity and *SIK2* copy-number amplifications in resistant ovarian cancer following neoadjuvant chemotherapy, uncovering synergistic effects of AP-1 and SIK2 inhibitors with chemotherapy.

Open vs minimally invasive radical trachelectomy in early-stage cervical cancer: International Radical Trachelectomy Assessment Study. G Salvo, PT. Ramirez, MM. Leitao, D Cibula, X Wu, H Falconer, J Persson, M Perrotta, BJ Mosgaard, A Kucukmetin, I Berlev, G Rendon, K Liu, M Vieira, ME Capilna, C Fotopoulou, G Baiocchi, D Kaidarova, R Ribeiro, S Pedra-Nobre, R Kocian, X Li, J Li, K Pálsdóttir, F Noll, S Rundle, E Ulrikh, Z Hu, M Gheorghe, S Saso, R Bolatbekova, A Tsunoda, B Pitcher, J Wu, D Urbauer, R Pareja. American Journal of Obstetrics and Gynecology 226 (1) 2022, 97.e1-97.e16, https://doi.org/10.1016/j.ajog.2021.08.029. https://www.sciencedirect.com/science/article/pii/S0002937821009637
Background Minimally invasive radical trachelectomy has emerged as an alternative to open radical hysterectomy for patients with early-stage cervical cancer desiring future fertility. Recent data suggest worse oncologic outcomes after minimally invasive radical hysterectomy than after open radical hysterectomy in stage I cervical cancer.
Objective We aimed to compare 4.5-year disease-free survival after open vs minimally invasive radical trachelectomy.
Study Design This was a collaborative, international retrospective study (International Radical Trachelectomy Assessment Study) of patients treated during 2005–2017 at 18 centers in 12 countries. Eligible patients had squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; had a preoperative tumor size of ≤2 cm; and underwent open or minimally invasive (robotic or laparoscopic) radical trachelectomy with nodal assessment (pelvic lymphadenectomy and/or sentinel lymph node biopsy). The exclusion criteria included neoadjuvant chemotherapy or preoperative pelvic radiotherapy, previous lymphadenectomy or pelvic retroperitoneal surgery, pregnancy, stage IA1 disease with lymphovascular space invasion, aborted trachelectomy (conversion to radical hysterectomy), or vaginal approach. Surgical approach, indication, and adjuvant therapy regimen were at the discretion of the treating institution. A total of 715 patients were entered into the study database. However, 69 patients were excluded, leaving 646 in the analysis. Endpoints were the 4.5-year disease-free survival rate (primary), 4.5-year overall survival rate (secondary), and recurrence rate (secondary). Kaplan-Meier methods were used to estimate disease-free survival and overall survival. A post hoc weighted analysis was performed, comparing the recurrence rates between surgical approaches, with open surgery being considered as standard and minimally invasive surgery as experimental.
Results Of 646 patients, 358 underwent open surgery, and 288 underwent minimally invasive surgery. The median (range) patient age was 32 (20–42) years for open surgery vs 31 (18–45) years for minimally invasive surgery (*P*=.11). Median (range) pathologic tumor size was 15 (0–31) mm for open surgery and 12 (0.8–40) mm for minimally invasive surgery (*P*=.33). The rates of pelvic nodal involvement were 5.3% (19 of 358 patients) for open surgery and 4.9% (14 of 288 patients) for minimally invasive surgery (*P*=.81). Median (range) follow-up time was 5.5 (0.20–16.70) years for open surgery and 3.1 years (0.02–11.10) years for minimally invasive surgery (*P*<.001). At 4.5 years, 17 of 358 patients (4.7%) with open surgery and 18 of 288 patients (6.2%) with minimally invasive surgery had recurrence (*P*=.40). The 4.5-year disease-free survival rates were 94.3% (95% confidence interval, 91.6–97.0) for open surgery and 91.5% (95% confidence interval, 87.6–95.6) for minimally invasive surgery (log-rank *P*=.37). Post hoc propensity score analysis of recurrence risk showed no difference between surgical approaches (*P*=.42). At 4.5 years, there were 6 disease-related deaths (open surgery, 3; minimally invasive surgery, 3) (log-rank *P*=.49). The 4.5-year overall survival rates were 99.2% (95% confidence interval, 97.6–99.7) for open surgery and 99.0% (95% confidence interval, 79.0–99.8) for minimally invasive surgery.
Conclusion The 4.5-year disease-free survival rates did not differ between open radical trachelectomy and minimally invasive radical trachelectomy. However, recurrence rates in each group were low. Ongoing prospective studies of conservative management of early-stage cervical cancer may help guide future management.

Lighting the Way for Improved Detection of Ovarian Cancer. Voelker R. JAMA. 2022;327(1):27. doi:10.1001/jama.2021.22960 https://jamanetwork.com/journals/jama/fullarticle/2787748
An imaging drug that can help surgeons identify ovarian cancer lesions that may otherwise go undetected has received FDA approval. Pafolacianine, marketed as Cytalux, is a targeted fluorescent imaging agent that illuminates ovarian cancer during surgery. Administered intravenously as little as an hour before surgery, pafolacianine binds to folate receptors, which often are overexpressed in ovarian cancer. Under fluorescent light, the drug illuminates cancerous tissue. The FDA has cleared a near-infrared fluorescence imaging system specifically for use with pafolacianine.



Currently, surgeons rely on preoperative imaging, visual inspection of tumors under normal light, or examination by touch to identify cancerous tissue, according to the FDA. "Complete removal of all malignant tissue is the goal of ovarian cancer surgery, however identifying all lesions can be challenging," Janos L. Tanyi, MD, PhD, associate professor of obstetrics and gynecology, University of Pennsylvania Perelman School of Medicine, and an investigator on the phase 2 and 3 studies, said in a statement from manufacturer On Target Laboratories, Inc, of West Lafayette, Indiana.

Tanyi and his colleagues evaluated pafolacianine in a phase 3 randomized, open-label clinical trial involving women who were scheduled to undergo ovarian cancer surgery. Among 134 women in the trial who received pafolacianine, 27% had cancerous lesions that conventional detection methods would have missed, according to the company statement. On Target Laboratories also noted that about 20% of cancerous lesions detected with pafolacianine were false-positives. False-negatives also may occur, the FDA added.

Common adverse events were infusion-related reactions including nausea, vomiting, abdominal pain, dyspepsia, chest discomfort, and hypersensitivity. Patients should avoid taking folate, folic acid, or folate-containing supplements within 48 hours of treatment with pafolacianine.

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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).