Ed's List

In The Know

Gyn Onc Literature of Significance

December 2021- November 2021

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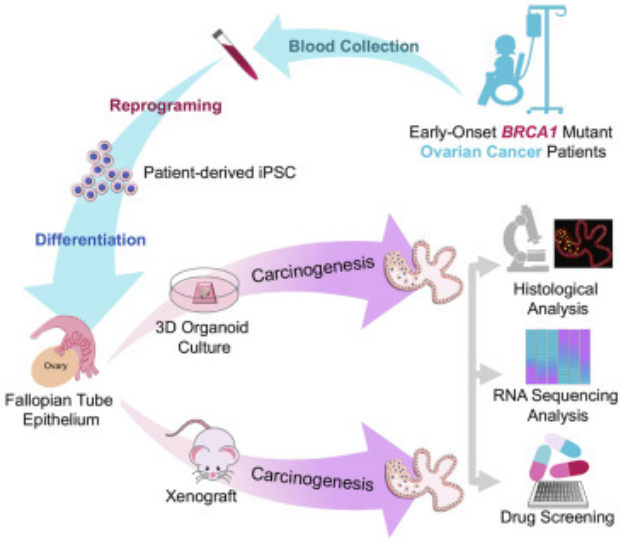
December

Human iPSC-derived fallopian tube organoids with BRCA1 mutation recapitulate early-stage carcinogenesis. N Yucer, R Ahdoot, MJ Workman, AH Laperle, MS Recouvreux, K Kurowski, DJ Naboulsi, V Liang, Y Qu, JT Plummer, SA Gayther, S Orsulic, BY Karlan, CN Svendsen. Cell Reports 37, 110146, 2021 DOI:https://doi.org/10.1016/j.celrep.2021.110146 https://www.cell.com/action/showPdf?pii=S2211-1247%2821%2901642-9



Germline pathogenic mutations in BReast CAncer (BRCA1) genes are thought to drive normal fallopian tube epithelial (FTE) cell transformation to high-grade serous ovarian cancer. No human models capture the sequence of events for disease initiation and progression. Here, we generate induced pluripotent stem cells (iPSCs) from healthy individuals and young ovarian cancer patients with germline pathogenic BRCA1 mutations (BRCA1mut). Following differentiation into FTE organoids, BRCA1mut lines exhibit cellular abnormalities consistent with neoplastic transformation compared to controls. BRCA1mut organoids show an increased production of cancer-specific proteins and survival following transplantation into mice. Organoids from women with the most aggressive ovarian cancer show the greatest pathology, indicating the potential value to predict clinical severity prior to disease onset. These human FTE organoids from BRCA1mut carriers provide a faithful physiological in vitro model of FTE lesion generation and early carcinogenesis. This platform can be used for personalized mechanistic and drug screening studies.

Genomic analyses of high-grade neuroendocrine gynecological malignancies reveal a unique mutational landscape and therapeutic vulnerabilities. H Mahdi, A Joehlin-Price, E Elishaev, A Dowlati, A Abbas. Molecular Oncology 15 (12), 2021 3545-3558. https://doi.org/10.1002/1878-0261.13057 https://febs.onlinelibrary.wiley.com/doi/10.1002/1878-0261.13057

High-grade neuroendocrine carcinoma of gynecologic origin (NEC-GYN) is a highly aggressive cancer that often affects young women. The clinical management of NEC-GYN is typically extrapolated from its counterpart, small cell carcinoma of the lung (SCLC), but, unfortunately, available therapies have limited benefit. In our NEC-GYN cohort, median progression-free survival (PFS) and overall survival (OS) were 1 and 12 months, respectively, indicating the highly lethal nature of this cancer. Our comprehensive genomic analyses unveiled that NEC-GYN harbors a higher mutational burden with distinct mutational landscapes from SCLC. We identified 14 cancer driver genes, including the most frequently altered KMT2C (100%), KNL1 (100%), NCOR2 (100%), and CCDC6 (93%) genes. Transcriptomic analysis identified several novel gene fusions; astonishingly, the MALAT1 lincRNA gene was found in ~20% of all fusion events in NEC-GYN. Furthermore, NEC-GYN exhibited a highly immunosuppressive state, intact RB1 expression, and was uniquely enriched with the YAP1high

molecular subtype. Our study identifies several potential therapeutic targets and suggests an urgent need to re-evaluate the treatment options for NEC-GYN.

Association Between Overall Survival and the Tendency for Cancer Programs to Administer Neoadjuvant Chemotherapy for Patients With Advanced Ovarian Cancer. A Melamed, JA Rauh-Hain, AA Gockley, R Nitecki, PT Ramirez, DL Hershman, N Keating, JD Wright. JAMA Oncol. 2021;7(12):1782–1790. doi:10.1001/jamaoncol.2021.4252 https://jamanetwork.com/journals/jamaoncology/article-abstract/2784404

Key Points

Question Was the differential adoption of neoadjuvant chemotherapy by US cancer centers for advanced-stage epithelial ovarian cancer associated with differences in overall survival?

Findings In this difference-in-differences comparative effectiveness research study that included 39 299 patients treated in 664 cancer programs, patients treated in programs that markedly increased administration of neoadjuvant chemotherapy achieved greater improvements in short-term mortality and equivalent gains in median overall survival compared with patients who were treated in programs that continued to use the treatment infrequently.

Meaning The study findings suggest that neoadjuvant chemotherapy may be an appropriate first-line treatment strategy for many patients with advanced-stage ovarian cancer.

Abstract

Importance Randomized clinical trials have found that, in patients with advanced-stage epithelial ovarian cancer, neoadjuvant chemotherapy has similar long-term survival and improved perioperative outcomes compared with primary cytoreductive surgery. Despite this, considerable controversy remains about the appropriate use of neoadjuvant chemotherapy, and the proportion of patients who receive this treatment varies considerably among cancer programs in the US.

Objective To evaluate the association between high levels of neoadjuvant chemotherapy administration and overall survival in patients with advanced ovarian cancer.

Design, Setting, and Participants This difference-in-differences comparative effectiveness analysis leveraged differential adoption of neoadjuvant chemotherapy in Commission on Cancer–accredited cancer programs in the US and included women with a diagnosis of stage IIIC and IV epithelial ovarian cancer between January 2004 and December 2015 who were followed up through the end of 2018. The data were analyzed between September 2020 and January 2021.

Exposures Treatment in a cancer program with high levels of neoadjuvant chemotherapy administration (more often than expected based on case mix) or in a program that continued to restrict its use after the 2010 publication of a clinical trial demonstrating the noninferiority of neoadjuvant chemotherapy compared with primary surgery for the treatment of patients with advanced ovarian cancer.

Main Outcomes and Measures Case mix–standardized median overall survival time and 1-year all-cause mortality assessed with a flexible parametric survival model.

Results We identified 19 562 patients (mean [SD] age, 63.9 [12.6] years; 3.2% Asian, 8.0% Black, 4.8% Hispanic, 82.5% White individuals) who were treated in 332 cancer programs that increased use of neoadjuvant chemotherapy from 21.7% in 2004 to 2009 to 42.2% in 2010 to 2015 and 19 737 patients (mean [SD] age, 63.5 [12.6] years; 3.1% Asian, 7.7% Black, 6.5% Hispanic, 81.8% White individuals) who were treated in 332 programs that marginally increased use of neoadjuvant chemotherapy (20.1% to 22.5%) over these periods. The standardized median overall survival times improved by similar magnitudes in programs with high (from 31.6 [IQR, 12.3-70.1] to 37.9 [IQR, 17.0-84.9] months; 6.3-month difference; 95% CI, 4.2-8.3) and low (from 31.4 [IQR, 12.1-67.2] to 36.8 [IQR, 15.0-80.3] months; 5.4-month difference, 95% CI, 3.5-7.3) use of neoadjuvant chemotherapy after 2010 (difference-in-differences, 0.9 months; 95% CI, −1.9 to 3.7). One-year mortality declined more in programs with high (from 25.6% to 19.3%; risk difference, −5.2%; 95% CI, −6.4 to −4.1) than with low (from 24.9% to 21.8%; risk difference, −3.2%, 95% CI, −4.3 to −2.0) use of neoadjuvant chemotherapy (difference-in-differences, −2.1%; 95% CI, −3.7 to −0.5).

Conclusions and Relevance In this comparative effectiveness research study, compared with cancer programs with low use of neoadjuvant chemotherapy, those with high use had similar improvements in median overall survival and larger declines in short-term mortality.

Preexisting TP53-Variant Clonal Hematopoiesis and Risk of Secondary Myeloid Neoplasms in Patients With High-grade Ovarian Cancer Treated With Rucaparib. TT.Kwan, AM Oza, AV Tinker, I Ray-Coquard, A Oaknin, C Aghajanian, D Lorusso, N Colombo, A Dean, J Weberpals, E Severson, L-T Vo, S Goble, L Maloney, T Harding, SH Kaufmann, JA Ledermann, RL Coleman, IA McNeish, KK Lin, EM Swisher. JAMA Oncol. 2021;7(12):1772–1781. doi:10.1001/jamaoncol.2021.4664 https://jamanetwork.com/journals/jamaoncology/article-abstract/2784883

Key Points

Question Are clonal hematopoiesis of indeterminate potential (CHIP) variants detected in peripheral blood cells (PBCs) before treatment with rucaparib associated with the risk of therapy-related myeloid neoplasms (t-MNs) after rucaparib treatment in patients with high-grade ovarian cancer?

Findings In this genetic association study, the prevalence of pretreatment TP53-variant CHIP with a variant allele frequency of 1% or higher in PBCs was significantly higher among patients with high-grade ovarian cancer who developed t-MNs after rucaparib therapy vs those who did not and was associated with longer prior exposure to platinum therapy.
Meaning The results of this study suggest that pretreatment TP53-variant CHIP detected at a variant allele frequency of 1% or higher in PBCs may be associated with development of t-MNs after rucaparib treatment.

Abstract

Importance A total of 1% to 3% of patients treated with a poly(adenosine diphosphate–ribose) polymerase inhibitor for high-grade ovarian cancer (HGOC) develop therapy-related myeloid neoplasms (t-MNs), which are rare but often fatal conditions. Although the cause of these t-MNs is unknown, clonal hematopoiesis of indeterminate potential (CHIP) variants can increase the risk of primary myeloid malignant neoplasms and are more frequent among patients with solid tumors.
Objectives To examine whether preexisting CHIP variants are associated with the development of t-MNs after rucaparib treatment and how these CHIP variants are affected by treatment.
Design, Setting, and Participants This retrospective genetic association study used peripheral blood cell (PBC) samples collected before rucaparib treatment from patients in the multicenter, single-arm ARIEL2 (Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer) (n = 491; between October 30, 2013, and August 9, 2016) and the multicenter, placebo-controlled, double-blind ARIEL3 (Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer) (n = 561; between April 7, 2014, and July 19, 2016), which tested rucaparib as HGOC therapy in the treatment and maintenance settings, respectively. The follow-up data cutoff date was September 1, 2019. Of 1052 patients in ARIEL2 and ARIEL3, PBC samples from 20 patients who developed t-MNs (cases) and 44 randomly selected patients who did not (controls) were analyzed for the presence of CHIP variants using targeted next-generation sequencing. Additional longitudinal analysis was performed on available ARIEL2 samples collected during treatment and at the end of treatment.
Main Outcomes and Measures Enrichment analysis of preexisting variants in 10 predefined CHIP-associated genes in cases relative to controls; association with clinical correlates.
Results Among 1052 patients (mean [SE] age, 61.7 [0.3] years) enrolled and dosed in ARIEL2 and ARIEL3, 22 (2.1%) developed t-MNs. The t-MNs were associated with longer overall exposure to prior platinum therapies (13.2 vs 9.0 months in ARIEL2, P = .04; 12.4 vs 9.6 months in ARIEL3, P = .003). The presence of homologous recombination repair gene variants in the tumor, either germline or somatic, was associated with increased prevalence of t-MNs (15 [4.1%] of 369 patients with HGOC associated with an HRR gene variant vs 7 [1.0%] of 683 patients with wild-type HGOC, P = .002). The prevalence of preexisting CHIP variants in TP53 but not other CHIP-associated genes at a variant allele frequency of 1% or greater was significantly higher in PBCs from cases vs controls (9 [45.0%] of 20 cases vs 6 [13.6%] of 44 controls, P = .009). TP53 CHIP was associated with longer prior exposure to platinum (mean 14.0 months of 15 TP53 CHIP cases vs 11.1 months of 49 non-TP53 CHIP cases; P = .02). Longitudinal analysis showed that preexisting TP53 CHIP variants expanded in patients who developed t-MNs.
Conclusions and Relevance The findings of this genetic association study suggest that preexisting TP53 CHIP variants may be associated with t-MNs after rucaparib treatment.

Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. S Banerjee, KN Moore, N Colombo, G Scambia, B-G Kim, A Oaknin, M Friedlander, A Lisyanskaya, A Floquet, A Leary, GS Sonke, C Gourley, A Oza, A González-Martín, C Aghajanian, WH Bradley, E Holmes, ES Lowe, P DiSilvestro. The Lancet Oncology 22 (12) 2021, 1721-1731, https://doi.org/10.1016/S1470-2045(21)00531-3. https://www.sciencedirect.com/science/article/pii/S1470204521005313)

Background There is a high unmet need for treatment regimens that increase the chance of long-term remission and possibly cure for women with newly diagnosed advanced ovarian cancer. In the primary analysis of SOLO1/GOG 3004, the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib significantly improved progression-free survival versus placebo in patients with a BRCA mutation; median progression-free survival was not reached. Here, we report an updated, post-hoc analysis of progression-free survival from SOLO1, after 5 years of follow-up.
Methods SOLO1 was a randomised, double-blind, placebo-controlled, phase 3 trial, done across 118 centres in 15 countries, that enrolled patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0–1 and with BRCA-mutated, newly diagnosed, advanced, high-grade serous or endometrioid ovarian cancer with a complete or partial clinical response after platinum-based chemotherapy. Patients were randomly assigned (2:1) via a web-based or interactive voice-response system to receive olaparib (300 mg twice daily) or placebo tablets orally as maintenance monotherapy for up to 2 years; randomisation was by blocks and was stratified according to clinical response after platinum-based chemotherapy. Patients, treatment providers, and data assessors were masked to group assignment. The primary endpoint was investigator-assessed progression-free survival. Efficacy is reported in the intention-to-treat population and safety in patients who received at least one dose of treatment. The data cutoff for this updated, post-hoc analysis was March 5, 2020. This trial is registered with ClinicalTrials.gov (NCT01844986) and is ongoing but closed to new participants.

Findings Between Sept 3, 2013, and March 6, 2015, 260 patients were randomly assigned to olaparib and 131 to placebo. The median treatment duration was 24·6 months (IQR 11·2–24·9) in the olaparib group and 13·9 months (8·0–24·8) in the placebo group; median follow-up was 4·8 years (2·8–5·3) in the olaparib group and 5·0 years (2·6–5·3) in the placebo group. In this post-hoc analysis, median progression-free survival was 56·0 months (95% CI 41·9–not reached) with olaparib versus 13·8 months (11·1–18·2) with placebo (hazard ratio 0·33 [95% CI 0·25–0·43]). The most common grade 3–4 adverse events were anaemia (57 [22%] of 260 patients receiving olaparib vs two [2%] of 130 receiving placebo) and neutropenia (22 [8%] vs six [5%]), and serious adverse events occurred in 55 (21%) of 260 patients in the olaparib group and 17 (13%) of 130 in the placebo group. No treatment-related adverse events that occurred during study treatment or up to 30 days after discontinuation were reported as leading to death. No additional cases of myelodysplastic syndrome or acute myeloid leukaemia were reported since the primary data cutoff, including after the 30-day safety follow-up period.
Interpretation For patients with newly diagnosed advanced ovarian cancer and a BRCA mutation, after, to our knowledge, the longest follow-up for any randomised controlled trial of a PARP inhibitor in this setting, the benefit derived from 2 years' maintenance therapy with olaparib was sustained beyond the end of treatment, extending median progression-free survival past 4·5 years. These results support the use of maintenance olaparib as a standard of care in this setting.

Minimally Invasive Compared With Open Hysterectomy in High-Risk Endometrial Cancer. B Segarra-Vidal, G Dinoi, A Zorrilla-Vaca, A Mariani, V Student, NA Garcia, A Llueca, A Abella, PT Ramirez. , Obstetrics & Gynecology: December 2021 - Volume 138 - Issue 6 - p 828-837 doi: 10.1097/AOG.0000000000004606 https://journals.lww.com/greenjournal/Fulltext/2021/12000/Minimally_Invasive_Compared_With_Open_Hysterectomy.2.aspx

OBJECTIVE: To compare disease-free survival between minimally invasive surgery and open surgery in patients with high-risk endometrial cancer.

METHODS: We conducted a multicentric, propensity-matched study of patients with high-risk endometrial cancer who underwent hysterectomy, bilateral salpingo-oophorectomy, and staging between January 1999 and June 2016 at two centers. High-risk endometrial cancer included grade 3 endometrioid, serous, clear cell, undifferentiated carcinoma or carcinosarcoma with any myometrial invasion. Patients were categorized a priori into two groups based on surgical approach, propensity scores were calculated based on potential confounders and groups were matched 1:1 using nearest neighbor technique. Cox hazard regression analysis and Kaplan-Meier curves evaluated the association of surgical technique with survival.

RESULTS: Of 626 eligible patients, 263 (42%) underwent minimally invasive surgery and 363 (58%) underwent open surgery. In the matched cohort, there were no differences in disease-free survival rates at 5 years between open (53.4% [95% CI 45.6–60.5%]) and minimally invasive surgery (54.6% [95% CI 46.6–61.8]; P=.82). Minimally invasive surgery was not associated with worse disease-free survival (hazard ratio [HR] 0.85, 95% CI 0.63–1.16; P=.30), overall survival (HR 1.04, 95% CI 0.73–1.48, P=.81), or recurrence rate (HR 0.99; 95% CI 0.69–1.44; P=.99) compared with open surgery. Use of uterine manipulator was not associated with worse disease-free survival (HR 1.01, 95% CI 0.65–1.58, P=.96), overall survival (HR 1.18, 95% CI 0.71–1.96, P=.53), or recurrence rate (HR 1.12, 95% CI 0.67–1.87; P=.66).

CONCLUSION: There was no difference in oncologic outcomes comparing minimally invasive and open surgery among patients with high-risk endometrial cancer.

The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. M Falcaro, A Castañon, B Ndlela, M Checchi, K Soldan, J Lopez-Bernal, L Elliss-Brookes, P Sasieni. The Lancet 398, (10316) 2084-2092, 2021 https://doi.org/10.1016/S0140-6736(21)02178-4 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02178-4/fulltext

Background Human papillomavirus (HPV) immunisation with a bivalent vaccine (Cervarix) was introduced in England, UK, in Sept 1, 2008: routine vaccination was offered to girls aged 12–13 years with a catch-up programme for females aged 14–18 years in 2008–10. We quantified the early effect of this immunisation programme on cervical cancer and cervical carcinoma in situ, namely grade 3 cervical intraepithelial neoplasia (CIN3), registrations.

Methods In this observational study, we used an extension of the age-period-cohort Poisson model to estimate the relative risk of cervical cancer in three vaccinated cohorts compared with earlier cohorts that were not eligible for HPV vaccination. Data from a population-based cancer registry were extracted on Jan 26, 2021, and were assessed for diagnoses of cervical cancer and CIN3 from Jan 1, 2006 to June 30, 2019 in women aged 20–64 years and who were a resident in England. We used three vaccinated cohorts to account for differences in the school year in which the vaccine was offered and its national coverage. Adjustment for confounding was made using information on changes in cervical screening policy and historical events that affected cervical cancer incidence. Results were compared across models with different adjustments for confounders.

Findings We used data from a total of 13·7 million-years of follow-up of women aged 20 years to younger than 30 years. The estimated relative reduction in cervical cancer rates by age at vaccine offer were 34% (95% CI 25–41) for age 16–18 years (school year 12–13), 62% (52–71) for age 14–16 years (school year 10–11), and 87% (72–94) for age 12–13 years

(school year 8), compared with the reference unvaccinated cohort. The corresponding risk reductions for CIN3 were 39% (95% CI 36–41) for those offered at age 16–18 years, 75% (72–77) for age 14–16 years, and 97% (96–98) for age 12–13 years. These results remained similar across models. We estimated that by June 30, 2019 there had been 448 (339–556) fewer than expected cervical cancers and 17 235 (15 919–18 552) fewer than expected cases of CIN3 in vaccinated cohorts in England.

Interpretation We observed a substantial reduction in cervical cancer and incidence of CIN3 in young women after the introduction of the HPV immunisation programme in England, especially in individuals who were offered the vaccine at age 12–13 years. The HPV immunisation programme has successfully almost eliminated cervical cancer in women born since Sept 1, 1995.

Recurrent Ovarian Cancer — Sculpting a Promising Future with Surgery.

GJ Gardner, DS Chi.

N Engl J Med 2021; 385:2187-2188 DOI: 10.1056/NEJMe2116353 https://www-nejm-org.ezproxy.uky.edu/doi/full/10.1056/NEJMe2116353

The combination of surgery and chemotherapy is a hallmark of the management of ovarian cancer. Although surgery is an integral component of management of this disease, its role in recurrent disease has been a topic of debate. After the collection of decades of data from retrospective studies, the results of prospective, randomized trials to guide management are now becoming available. In this issue of the *Journal*, Harter et al. report the results of the Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP) III trial, a randomized, phase 3 trial that evaluated secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian cancer. A greater benefit with respect to overall survival and progression-free survival was seen among patients assigned to undergo secondary cytoreductive surgery and then receive chemotherapy than among patients assigned to receive chemotherapy alone. Furthermore, baseline prognostic factors did not identify a subgroup of patients without benefit. These results are consistent with those of the Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC-1) trial, which showed a median progression-free survival of 17.4 months among patients who underwent secondary cytoreductive surgery and 11.9 months among those who did not undergo surgery (hazard ratio for disease progression, 0.58; 95% confidence interval, 0.45 to 0.74). Final results for overall survival in the SOC-1 trial are not yet mature. The results of the SOC-1 trial contradict those of the Gynecologic Oncology Group (GOG)–0213 trial, which showed no significant difference with respect to progression-free or overall survival between patients who underwent secondary cytoreductive surgery and those who did not, other than in subgroup analyses. Whereas the DESKTOP III, SOC-1, and GOG-0213 trials were randomized, controlled trials evaluating surgery for the first relapse of platinum-sensitive ovarian cancer, three key differences in trial design are relevant for the interpretation of their results: patient selection, surgical quality control, and use of antiangiogenic agents. The DESKTOP III trial used carefully developed criteria for patient selection, building on the DESKTOP I and DESKTOP II trials, to define and validate criteria that would predict successful complete gross resection. The SOC-1 trial used the iMODEL (international model) to predict the likelihood of complete gross resection at enrollment. In contrast, patients were eligible for the GOG-0213 trial if the investigator deemed that complete gross resection would be possible; the GOG-0213 trial was a randomized trial that evaluated secondary cytoreductive surgery, and no criteria for the selection of participants in such trials had been established at the time. Notably, all three trials showed a survival benefit with secondary cytoreductive surgery when complete gross resection was achieved. The results of the GOG-0213 trial indicate that secondary cytoreductive surgery does not translate to an overall survival benefit in the absence of standardized criteria for patient selection that are predictive of complete gross resection. Refined selection criteria are central to the interpretation of trial results and application to clinical practice. Other centers have shown criteria for patient selection that are reproducible and highly predictive of complete gross resection. Although these criteria have not been tested prospectively, they allow for more expanded eligibility for secondary cytoreductive surgery than the criteria used in the DESKTOP III trial, with patient selection not contingent on the surgical outcome of the primary cytoreduction, but instead incorporating disease distribution at recurrence. Surgical quality control is another key element of the designs of these three trials. Complete gross resection was achieved in 75.5% of patients in the DESKTOP III trial, the median duration of surgery was 3.7 hours, the median estimated blood loss was 250 ml, and the incidence of adverse events related to surgery was low. Trial centers had experience in ovarian cancer studies and had participated in surgical trials in this field. Although the generalizability of technical skill at large-volume centers to other practice environments is questionable, surgery can be a watershed event in the downstream course of disease in women with ovarian cancer, and these women may benefit from treatment at centers with proven surgical excellence. Whereas some secondary cytoreductive surgeries are small, localized procedures, in the DESKTOP III trial, 36% of patients underwent bowel resection, 17% diaphragm surgery, 13% splenectomy, and 5% partial hepatectomy; these surgeries underscore the importance of both the surgical volume and the technical skill needed to successfully perform secondary cytoreductive surgery. In contrast to the DESKTOP III trial, the GOG-0213 trial was largely a chemotherapy trial with embedded randomization to surgery and did not specify surgical quality controls. In the GOG-0213 trial, 84% of patients received an antiangiogenic agent, as compared with a minority in the other trials. Do the results of secondary cytoreductive surgery performed in the context of a trial evaluating antiangiogenic therapy translate to the treatment of recurrent ovarian cancer as a whole? The DESKTOP III trial showed the benefit of secondary cytoreductive surgery regardless of previous antiangiogenic therapy, and now the growing use of poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors in combination with secondary cytoreductive surgery deserves further study. We practice in an era of expanded molecular

understanding of tumor biology and an ever-increasing opportunity for targeted therapy. If we truly seek to cure ovarian cancer, we need to bring our entire toolbox to the table. We need to use precision in the selection of medical and surgical options — the right treatment for the right patient. We commend the authors, investigators, and patients who participated in the DESKTOP III trial for their roles in a high-quality trial in which personalized medicine does not just apply to medical therapy, but to surgical therapy as well. Now is the time to move toward a cure for ovarian cancer and to use all of our best talents to do it.

Randomized Trial of Cytoreductive Surgery for Relapsed Ovarian Cancer. P Harter, J Sehouli, I Vergote, G Ferron, A Reuss, W Meier, S Greggi, BJ Mosgard, F Selle, F Guyon, C Pomel, F Lécuru, R Zang, E Avall-Lundqvist, J-W Kim, J Ponce, F Raspagliesi, G Kristensen, J-M Classe, P Hillemanns, P Jensen, A Hasenburg, S Ghaem-Maghami, MR Mirza, B Lund, A Reinthaller, A Santaballa, A Olaitan, F Hilpert, A du Bois. N Engl J Med 2021; 385:2123-2131 DOI: 10.1056/NEJMoa2103294 https://www.nejm.org/doi/full/10.1056/NEJMoa2103294

BACKGROUND Treatment for patients with recurrent ovarian cancer has been mainly based on systemic therapy. The role of secondary cytoreductive surgery is unclear.

METHODS We randomly assigned patients with recurrent ovarian cancer who had a first relapse after a platinum-free interval (an interval during which no platinum-based chemotherapy was used) of 6 months or more to undergo secondary cytoreductive surgery and then receive platinum-based chemotherapy or to receive platinum-based chemotherapy alone. Patients were eligible if they presented with a positive Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score, defined as an Eastern Cooperative Oncology Group performance-status score of 0 (on a 5-point scale, with higher scores indicating greater disability), ascites of less than 500 ml, and complete resection at initial surgery. A positive AGO score is used to identify patients in whom a complete resection might be achieved. The primary end point was overall survival. We also assessed quality of life and prognostic factors for survival.

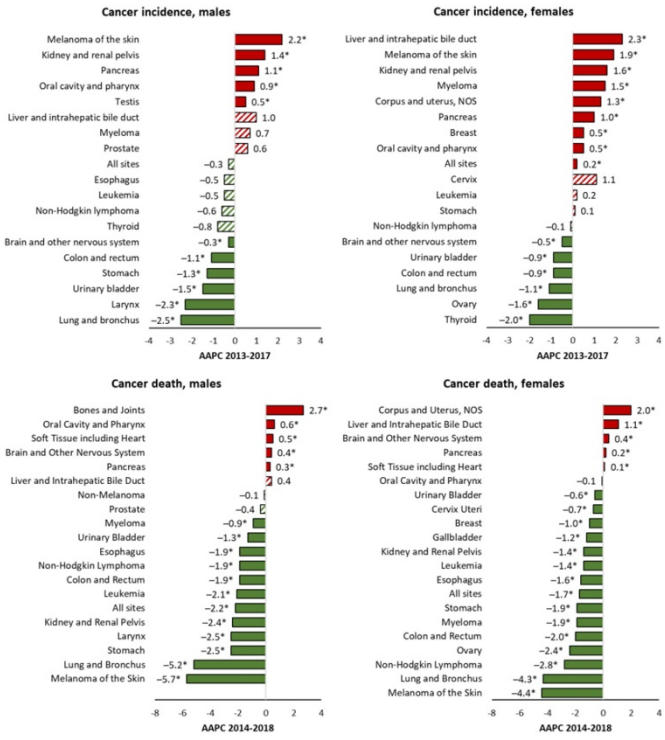
RESULTS A total of 407 patients underwent randomization: 206 were assigned to cytoreductive surgery and chemotherapy, and 201 to chemotherapy alone. A complete resection was achieved in 75.5% of the patients in the surgery group who underwent the procedure. The median overall survival was 53.7 months in the surgery group and 46.0 months in the no-surgery group (hazard ratio for death, 0.75; 95% confidence interval, 0.59 to 0.96; P=0.02). Patients with a complete resection had the most favorable outcome, with a median overall survival of 61.9 months. A benefit from surgery was seen in all analyses in subgroups according to prognostic factors. Quality-of-life measures through 1 year of follow-up did not differ between the two groups, and we observed no perioperative mortality within 30 days after surgery.

CONCLUSIONS In women with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone.

Annual Report to the Nation on the Status of Cancer, Part 1. Farhad Islami, , Elizabeth M Ward, Hyuna Sung, Kathleen A Cronin, Florence K L Tangka, Recinda L Sherman, Jingxuan Zhao, Robert N Anderson, S Jane Henley, K Robin Yabroff, Ahmedin Jemal, Vicki B Benard. National Cancer Statistics, *JNCI:* 113, (12) 2021, 1648–1669, https://doi.org/10.1093/jnci/djab131 https://academic.oup.com/jnci/article/113/12/1648/6312532

Background The American Cancer Society, Centers for Disease Control and Prevention, National Cancer Institute, and North American Association of Central Cancer Registries collaborate to provide annual updates on cancer incidence and mortality and trends by cancer type, sex, age group, and racial/ethnic group in the United States. In this report, we also examine trends in stage-specific survival for melanoma of the skin (melanoma). **Methods** Incidence data for all cancers from 2001 through 2017 and survival data for melanoma cases diagnosed during 2001-2014 and followed-up through 2016 were obtained from the Centers for Disease Control and Prevention- and National Cancer Institute-funded population-based cancer registry programs compiled by the North American Association of Central Cancer Registries. Data on cancer deaths from 2001 to 2018 were obtained from the National Center for Health Statistics' National Vital Statistics System. Trends in age-standardized incidence and death rates and 2-year relative survival were estimated by joinpoint analysis, and trends in incidence and mortality were expressed as average annual percent change (AAPC) during the most recent 5 years (2013-2017 for incidence and 2014-2018 for mortality).

Results Overall cancer incidence rates (per 100 000 population) for all ages during 2013-2017 were 487.4 among males and 422.4 among females. During this period, incidence rates remained



stable among males but slightly increased in females (AAPC = 0.2%, 95% confidence interval [CI] = 0.1% to 0.2%). Overall cancer death rates (per 100 000 population) during 2014-2018 were 185.5 among males and 133.5 among females. During this period, overall death rates decreased in both males (AAPC = −2.2%, 95% CI = −2.5% to −1.9%) and females (AAPC = −1.7%, 95% CI = −2.1% to −1.4%); death rates decreased for 11 of the 19 most common cancers among males and for 14 of the 20 most common cancers among females, but increased for 5 cancers in each sex. During 2014-2018, the declines in death rates accelerated for lung cancer and melanoma, slowed down for colorectal and female breast cancers, and leveled off for prostate cancer. Among children younger than age 15 years and adolescents and young adults aged 15-39 years, cancer death rates continued to decrease in contrast to the increasing incidence rates. Two-year relative survival for distant-stage skin melanoma was stable for those diagnosed during 2001-2009 but increased by 3.1% (95% CI = 2.8% to 3.5%) per year for those diagnosed during 2009-2014, with comparable trends among males and females.
Conclusions Cancer death rates in the United States continue to decline overall and for many cancer types, with the decline accelerated for lung cancer and melanoma. For several other major cancers, however, death rates continue to increase or previous declines in rates have slowed or ceased. Moreover, overall incidence rates continue to increase among females, children, and adolescents and young adults. These findings inform efforts related to prevention, early detection, and treatment and for broad and equitable implementation of effective interventions, especially among under resourced populations.
Uterine cancer is reported as an exception to the declines reported.

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