Ed's List
April 2022

In The Know
Gyn Onc Literature of Significance

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April

Ovarian cancer immunogenicity is governed by a narrow subset of progenitor tissue-resident memory T cells. CM Anadon, X Yu, K Hänggi, S Biswas, RA Chaurio, A Martin, KK. Payne, G Mandal, P Innamarato, CM Harro, JA Mine, KB Sprenger, C Cortina, JJ Powers, TL Costich, BA Perez, CD Gatenbee, S Prabhakaran, D Marchion, MHM Heemskerk, TJ Curiel, AR Anderson, RM Wenham, PC Rodriguez, JR Conejo-Garcia. Cancer Cell, 2022, https://doi.org/10.1016/j.ccell.2022.03.008
(https://www.sciencedirect.com/science/article/pii/S1535610822001234)

Despite repeated associations between T cell infiltration and outcome, human ovarian cancer remains poorly responsive to immunotherapy. We report that the hallmarks of tumor recognition in ovarian cancer-infiltrating T cells are primarily restricted to tissue-resident memory (TRM) cells. Single-cell RNA/TCR/ATAC sequencing of 83,454 CD3+CD8+CD103+CD69+ TRM cells and immunohistochemistry of 122 high-grade serous ovarian cancers shows that only progenitor (TCF1low) tissue-resident T cells (TRMstem cells), but not recirculating TCF1+ T cells, predict ovarian cancer outcome. TRMstem cells arise from transitional recirculating T cells, which depends on antigen affinity/persistence, resulting in oligoclonal, trogocytic, effector lymphocytes that eventually become exhausted. Therefore, ovarian cancer is indeed an immunogenic disease, but that depends on ~13% of CD8+ tumor-infiltrating T cells (~3% of CD8+ clonotypes), which are primed against high-affinity antigens and maintain waves of effector TRM-like cells. Our results define the signature of relevant tumor-reactive T cells in human ovarian cancer, which could be applicable to other tumors with unideal mutational burden.

Highlights

1. Only TRM TILs show clonal enrichment and effector activity in ovarian cancer
2. Stem-like TRM cells replenish effector TRM cells as they become exhausted
3. Intra-epithelial TCF1^{low} TRM TILs predict human ovarian cancer outcome
4. Sustained ovarian cancer antigen recognition depends on ~13% of CD8+ TILs

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Hospital-Administered Cancer Therapy Prices for Patients With Private Health Insurance. R Xiao, JS Ross, CP Gross, SB Dusetzina, JM McWilliams, RKV Sethi, VK Rathi. JAMA Intern Med. Published online April 18, 2022. doi:10.1001/jamainternmed.2022.1022 https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2791386

Key Points

Question How much do US hospitals mark up the price of parenteral cancer therapies for patients with private health insurance?

Findings This cross-sectional study examined private payer–specific prices for 25 commonly used parenteral cancer therapies at 61 National Cancer Institute–designated cancer centers. Median price markups across centers ranged from approximately 120% (sipuleucel-T) to 630% (leuprolide) of estimated hospital acquisition costs.

Meaning The findings of this study suggest that, to reduce the financial burden of cancer treatment for patients, institution of public policies to discourage or prevent excessive hospital price markups on parenteral chemotherapeutics may be beneficial.

Abstract

Importance The federal Hospital Price Transparency final rule, which became effective in 2021, requires hospitals to publicly disclose payer-specific prices for drugs. However, little is known about hospital markup prices for parenterally administered therapies.

Objective To assess the extent of price markup by hospitals on parenterally administered cancer therapies and price variation among hospitals and between payers at each hospital.

Design, Setting, and Participants A cross-sectional analysis was conducted of private payer–specific negotiated prices for the top 25 parenteral (eg, injectable or infusible) cancer therapies by Medicare Part B spending in 2019 using publicly available hospital price transparency files. Sixty-one National Cancer Institute (NCI)–designated cancer centers providing clinical care to adults with cancer were included. The study was conducted from April 1 to October 15, 2021.

Exposures Estimated hospital acquisition costs for each cancer therapy using participation data from the federal 340B Drug Pricing Program.

Main Outcomes and Measures The primary outcome was hospital price markup for each cancer therapy in excess of estimated acquisition costs. Secondary outcomes were the extent of across-center price ratios, defined as the ratio between the 90th percentile and 10th percentile median prices across centers, and within-center price ratios, defined as the ratio between the 90th percentile and 10th percentile prices between payers at each center.

Results Of 61 NCI-designated cancer centers, 27 (44.3%) disclosed private payer–specific prices for at least 1 top-selling cancer therapy as required by federal regulations. Median drug price markups across all centers and payers ranged between 118.4% (sipuleucel-T) and 633.6% (leuprolide). Across-center price ratios ranged between 2.2 (pertuzumab) and 15.8 (leuprolide). Negotiated prices also varied considerably between payers at the same center; median within-center price ratios for cancer therapies ranged from 1.8 (brentuximab) to 2.5 (bevacizumab).

Conclusions and Relevance Most NCI-designated cancer centers did not publicly disclose payer-specific prices for cancer therapies as required by federal regulation. The findings of this cross-sectional study suggest that, to reduce the financial burden of cancer treatment for patients, institution of public policies to discourage or prevent excessive hospital price markups on parenteral chemotherapeutics might be beneficial.

Phosphate dysregulation via the XPR1–KIDINS220 protein complex is a therapeutic vulnerability in ovarian cancer. DP Bondeson, BR Paolella, A Asfaw, MV Rothberg, TA Skipper, C Langan, G Mesa, A Gonzalez, LE Surface, K Ito, M Kazachkova, WN Colgan, A Warren, JM Dempster, JM Krill-Burger, M Ericsson, AA Tang, I Fung, ES Chambers, M Abdusamad, N Dumont, JG Doench, F Piccioni, DE Root, J Boehm, WC Hahn, M Mannstadt, JM McFarland, F Vazquez, TR Golub. Nat Cancer (2022). https://doi.org/10.1038/s43018-022-00360-7 https://www.nature.com/articles/s43018-022-00360-7#citeas

Despite advances in precision medicine, the clinical prospects for patients with ovarian and uterine cancers have not substantially improved. Here, we analyzed genome-scale CRISPR–Cas9 loss-of-function screens across 851 human cancer cell lines and found that frequent overexpression of SLC34A2—encoding a phosphate importer—is correlated with sensitivity to loss of the phosphate exporter XPR1, both in vitro and in vivo. In patient-derived tumor samples, we observed frequent PAX8-dependent overexpression of SLC34A2, XPR1 copy number amplifications and XPR1 messenger RNA overexpression. Mechanistically, in SLC34A2-high cancer cell lines, genetic or pharmacologic inhibition of XPR1-dependent phosphate efflux leads to the toxic accumulation of intracellular phosphate. Finally, we show that XPR1 requires the novel partner protein KIDINS220 for proper cellular localization and activity, and that disruption of this protein complex results in acidic “vacuolar” structures preceding cell death. These data point to the XPR1–KIDINS220 complex and phosphate dysregulation as a therapeutic vulnerability in ovarian cancer.

Integrated Analysis of Ovarian Juvenile Granulosa Cell Tumors Reveals Distinct Epigenetic Signatures and Recurrent TERT Rearrangements. T Vougiouklakis, K Zhu, V Vasudevaraja, J Serrano, G Shen, RL Linn, X Feng, S Chiang, JE Barroeta, KM Thomas, LE Schwartz, PS Shukla, A Malpica, E Oliva, P Cotzia, DF DeLair, M Snuderl, G Jour. Clin Cancer Res 15 April 2022; 28 (8): 1724–1733. https://doi.org/10.1158/1078-0432.CCR-21-3394 https://aacrjournals.org/clincancerres/article-abstract/28/8/1724/694167/Integrated-Analysis-of-Ovarian-Juvenile-Granulosa?redirectedFrom=fulltext

Purpose: Adult granulosa cell tumor (AGCT) is characterized by the somatic FOXL2 p.C134W mutation, and recurrences have been associated with TERT promoter and KMT2D-truncating mutations. Conversely, the molecular underpinnings of the rare juvenile granulosa cell tumor (JGCT) have not been well elucidated. To this end, we applied a tumor-only integrated approach to investigate the genomic, transcriptomic, and epigenomic landscape of 31 JGCTs to identify putative oncogenic drivers.

Experimental Design: Multipronged analyses of 31 JGCTs were performed utilizing a clinically validated next-generation sequencing (NGS) panel targeting 580 cancer-related genes for genomic interrogation, in addition to targeted RNA NGS for transcriptomic exploration. Genome-wide DNA methylation profiling was conducted using an Infinium Methylation EPIC array targeting 866,562 CpG methylation sites.

Results: We identified frequent KMT2C-truncating mutations along with other mutated genes implicated in the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, in addition to previously reported hotspot AKT1

and DICER1 mutations. Targeted transcriptome sequencing revealed recurrent TERT rearrangements (13%) involving partners CLPTM1L or DROSHA, and differential gene expression analysis showed FGFR1 upregulation in the TERT non-rearranged JGCTs under direct promoter control. Genome-wide DNA methylation rendered a clear delineation between AGCTs and JGCTs at the epigenomic level, further supporting its diagnostic utility in distinguishing among these tumors.
Conclusions: This is the largest comprehensive molecular study of JGCTs, where we further expand our current understanding of JGCT pathogenesis and demonstrate putative oncogenic drivers and TERT rearrangements in a subset of tumors. Our findings further offer insights into possible targeted therapies in a rare entity.

Can miRNAs be useful biomarkers in improving prognostic stratification in endometrial cancer patients? An update review. G Ravegnini, F Gorini, E De Crescenzo, A De Leo, D De Base, M Di Stanislao, P Hrelia, S Angelini, P De Iaco, A Myriam Perrone. Int. J. Cancer. 2022; 150(7): 1077- 1090. doi:10.1002/ijc.33857 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33857
Endometrial cancer (EC) is the most common gynecological cancer, with annual incidence rates in Western countries ranging between 15 and 25 per 100 000 women. About 15% to 20% of patients with EC have high-risk disease and follow an aggressive clinical course. Unfortunately, the assessment of histologic parameters is poorly reproducible and conventional clinicopathological and molecular features do not reliably predict either the patient's response to the available treatments or the definition of personalized therapeutic approaches. In this context, the identification of novel diagnostic and prognostic biomarkers, which can be integrated in the current classification schemes, represents an unmet clinical need and an important challenge. miRNAs are key players in cancer by regulating the expression of specific target genes. Their role in EC, in association with clinical and prognostic tumor biomarkers, has been investigated but, so far, with little consensus among the studies. The present review aims to describe the recent advances in miRNAs research in EC taking into consideration the current classification schemes and to highlight the most promising miRNAs. Finally, a perspective point of view sheds light on the challenges ahead in the landscape of EC.

Validation analysis of the novel imaging-based prognostic radiomic signature in patients undergoing primary surgery for advanced high-grade serous ovarian cancer (HGSOC). C Fotopoulou, A Rockall, H Lu, P Lee, G Avesani, L Russo, F Petta, B Ataseven, KU Waltering, JA Koch, WR Crum, P Cunnea, F Heitz, P Harter, EO Aboagye, A du Bois, S Prader**.** Br J Cancer. 2022 Apr;126(7):1047-1054. doi: 10.1038/s41416-021-01662-w. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8979975/
Background Predictive models based on radiomics features are novel, highly promising approaches for gynaecological oncology. Here, we wish to assess the prognostic value of the newly discovered Radiomic Prognostic Vector (RPV) in an independent cohort of high-grade serous ovarian cancer (HGSOC) patients, treated within a Centre of Excellence, thus avoiding any bias in treatment quality.
Methods RPV was calculated using standardised algorithms following segmentation of routine preoperative imaging of patients (n = 323) who underwent upfront debulking surgery (01/2011-07/2018). RPV was correlated with operability, survival and adjusted for well-established prognostic factors (age, postoperative residual disease, stage), and compared to previous validation models.
Results The distribution of low, medium and high RPV scores was 54.2% (n = 175), 33.4% (n = 108) and 12.4% (n = 40) across the cohort, respectively. High RPV scores independently associated with significantly worse progression-free survival (PFS) (HR = 1.69; 95% CI:1.06–2.71; P = 0.038), even after adjusting for stage, age, performance status and residual disease. Moreover, lower RPV was significantly associated with total macroscopic tumour clearance (OR = 2.02; 95% CI:1.56–2.62; P = 0.00647).
Conclusions RPV was validated to independently identify those HGSOC patients who will not be operated tumour-free in an optimal setting, and those who will relapse early despite complete tumour clearance upfront. Further prospective, multicentre trials with a translational aspect are warranted for the incorporation of this radiomics approach into clinical routine.

Tumor FAK orchestrates immunosuppression in ovarian cancer via the CD155/TIGIT axis.
D Ozmadenci, JSS Narayanan, J Andrew, M Ojalill, AM Barrie, S Jiang, S Iyer, XL Chen, M Rose, V Estrada, A Molinolo, T Bertotto, Z Mikulski, MC McHale, RR White, DC Connolly, JA Pachter, VK Kuchroo, DG Stupack, DD Schlaepfer. PNAS 2022 119 (17) e2117065119 https://doi.org/10.1073/pnas.2117065119

Significance

High-grade serous ovarian carcinoma (HGSOC) is an immunotherapy-resistant lethal cancer. An HGSOC hallmark is elevated checkpoint pathway ligand expression that limits antitumor immune responses. Computational, preclinical, and patient tumor multiplexed analyses revealed that tumor-associated focal adhesion kinase (FAK) activation regulates CD155 expression, a checkpoint ligand for TIGIT (T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains). Using an aggressive mouse ovarian tumor model, we find that combined oral FAK inhibitor plus function-blocking TIGIT antibody immunotherapy reduced tumor burden, prolonged mouse survival, and led to immune cell

activation and tertiary lymphoid structure formation, hallmarks of an antitumor immune response. As FAK is commonly overexpressed in HGSOC tumors, targeting FAK and TIGIT may limit tumor immune evasion.

Abstract

High-grade serous ovarian cancer (HGSOC) is a lethal malignancy characterized by an immunosuppressive tumor microenvironment containing few tumor infiltrating lymphocytes (TILs) and an insensitivity to checkpoint inhibitor immunotherapies. Gains in the PTK2 gene encoding focal adhesion kinase (FAK) at Chr8 q24.3 occur in ~70% of HGSOC tumors, and elevated FAK messenger RNA (mRNA) levels are associated with poor patient survival. Herein, we show that active FAK, phosphorylated at tyrosine-576 within catalytic domain, is significantly increased in late-stage HGSOC tumors. Active FAK costained with CD155, a checkpoint receptor ligand for TIGIT (T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains), in HGSOC tumors and a selective association between FAK and TIGIT checkpoint ligands were supported by patient transcriptomic database analysis. HGSOC tumors with high FAK expression were associated with low CD3 mRNA levels. Accordingly, late-stage tumors showed elevated active FAK staining and significantly lower levels of CD3+ TILs. Using the KMF (Kras, Myc, FAK) syngeneic ovarian tumor model containing spontaneous PTK2 (FAK) gene gains, the effects of tumor intrinsic genetic or oral small molecule FAK inhibitior (FAKi; VS-4718) were evaluated in vivo. Blocking FAK activity decreased tumor burden, suppressed ascites KMF-associated CD155 levels, and increased peritoneal TILs. The combination of FAKi with blocking TIGIT antibody (1B4) maintained elevated TIL levels and reduced TIGIT+ T regulatory cell levels, prolonged host survival, increased CXCL13 levels, and led to the formation of omental tertiary lymphoid structures. Collectively, our studies support FAK and TIGIT targeting as a rationale immunotherapy combination for HGSOC.

PGC1α/β Expression Predicts Therapeutic Response to Oxidative Phosphorylation Inhibition in Ovarian Cancer. C Ghilardi, C Moreira-Barbosa, L Brunelli, P Ostano, N Panini, M Lupi, A Anastasia, F Fiordaliso, M Salio, L Formenti, M Russo, E Arrigoni, F Chiaradonna, G Chiorino, G Draetta, JR Marszalek, CP Vellano, R Pastorelli, MR Bani, A Decio, R Giavazzi. Cancer Res 1 April 2022; 82 (7): 1423–1434. https://doi.org/10.1158/0008-5472.CAN-21-1223
https://aacrjournals.org/cancerres/article/82/7/1423/694053/PGC1-Expression-Predicts-Therapeutic-Response-to

Ovarian cancer is the deadliest gynecologic cancer, and novel therapeutic options are crucial to improve overall survival. Here we provide evidence that impairment of oxidative phosphorylation (OXPHOS) can help control ovarian cancer progression, and this benefit correlates with expression of the two mitochondrial master regulators PGC1α and PGC1β. In orthotopic patient-derived ovarian cancer xenografts (OC-PDX), concomitant high expression of PGC1α and PGC1β (PGC1α/β) fostered a unique transcriptional signature, leading to increased mitochondrial abundance, enhanced tricarboxylic acid cycling, and elevated cellular respiration that ultimately conferred vulnerability to OXPHOS inhibition. Treatment with the respiratory chain complex I inhibitor IACS-010759 caused mitochondrial swelling and ATP depletion that consequently delayed malignant progression and prolonged the lifespan of high PGC1α/β-expressing OC-PDX-bearing mice. Conversely, low PGC1α/β OC-PDXs were not affected by IACS-010759, thus pinpointing a selective antitumor effect of OXPHOS inhibition. The clinical relevance of these findings was substantiated by analysis of ovarian cancer patient datasets, which showed that 25% of all cases displayed high PGC1α/β expression along with an activated mitochondrial gene program. This study endorses the use of OXPHOS inhibitors to manage ovarian cancer and identifies the high expression of both PGC1α and β as biomarkers to refine the selection of patients likely to benefit most from this therapy.
Significance: OXPHOS inhibition in ovarian cancer can exploit the metabolic vulnerabilities conferred by high PGC1α/β expression and offers an effective approach to manage patients on the basis of PGC1α/β expression.

Risk of de novo cancer after premenopausal bilateral oophorectomy. N Huo, CY Smith, LG Rocca, WA Rocca, MM Mielke. American Journal of Obstetrics and Gynecology, 226, (4) 2022 539.e1-539.e16, https://doi.org/10.1016/j.ajog.2021.10.040.
https://www.sciencedirect.com/science/article/pii/S0002937821012229?via%3Dihub

Background Hysterectomy is one of the most frequent gynecologic surgeries in the United States. Women undergoing hysterectomy are commonly offered bilateral oophorectomy for ovarian and breast cancer prevention. Although bilateral oophorectomy may dramatically reduce the risk of gynecologic cancers, some studies suggested that bilateral oophorectomy may be associated with an increased risk of other types of cancer, such as lung cancer and colorectal cancer. However, the results are conflicting.
Objective To study the association between bilateral oophorectomy and the risk of subsequent cancer of any type.
Study Design This population-based cohort study included all premenopausal women who underwent bilateral oophorectomy for a nonmalignant indication before the age of 50, between January 1, 1988 and December 31, 2007 in Olmsted County, Minnesota, and a random sample of age-matched (±1 year) referent women who did not undergo bilateral oophorectomy. Women with cancer before oophorectomy (or index date) or within 6 months after the index date were excluded. Time-to-event analyses were performed to assess the risk of de novo cancer. Cancer diagnosis and type were confirmed using medical record review.

Results Over a median follow-up of 18 years, the risk of any cancer did not significantly differ between the 1562 women who underwent bilateral oophorectomy before natural menopause and the 1610 referent women (adjusted hazard ratio, 0.82; 95% confidence interval, 0.66–1.03). However, women who underwent bilateral oophorectomy had a decreased risk of gynecologic cancers (adjusted hazard ratio, 0.15; 95% confidence interval, 0.06–0.34) but not of nongynecologic cancers (adjusted hazard ratio, 0.99; 95% confidence interval, 0.78–1.26). In particular, the risk of breast cancer, gastrointestinal cancer, and lung cancer did not differ between these 2 cohorts. Use of estrogen therapy through the age of 50 years in women who underwent bilateral oophorectomy did not modify the results.

Conclusion Women who underwent bilateral oophorectomy before menopause have a reduced risk of gynecologic cancer but not of other types of cancer including breast cancer. Women at average risk of ovarian cancer should not consider bilateral oophorectomy for the prevention of breast cancer or other nongynecologic cancers.

Oral Contraceptives and BRCA Cancer: A Balancing Act. J Kotsopoulos. JNCI: Journal of the National Cancer Institute, Volume 114, Issue 4, April 2022, Pages 483–484, https://doi.org/10.1093/jnci/djac006 https://academic.oup.com/jnci/article/114/4/483/6512065?login=true

Women who inherit a pathogenic mutation in the BRCA1 or BRCA2 gene face high lifetime risks of developing breast and ovarian (or fallopian tube) cancer. It is suggested that these women are also predisposed to endometrial cancer (particularly the aggressive serous subtype), albeit with a much lower risk than that of breast or ovarian cancer. The impact of modifiable exposures on cancer risk, particularly exogenous hormones, including oral contraceptives and hormone replacement therapy (HRT), has been studied extensively. They contain similar hormone profiles, although the doses tend to be much higher in oral contraceptive preparations .

In women with mutations, an increased risk of breast cancer with use of estrogen plus progesterone (but not estrogen alone) HRT has been described; however, the impact of oral contraceptive use is uncertain. In the general population, oral contraceptives transiently increase the risk of breast cancer, but the absolute risk is small given the typically young age of the user. This is not so for BRCA mutation carriers, who typically develop breast cancer at a young age. Complicating matters further, oral contraceptives have a protective effect against ovarian cancer (irrespective of mutation status) and are associated with a 50% (or more) reduction in risk with 5 years of use among BRCA mutation carriers. Prophylactic bilateral mastectomy is the most effective option to manage breast cancer risk in these high-risk women; however, many (if not most) opt for intensified screening with annual MRI imaging. Preventive bilateral salpingo-oophorectomy is recommended (by age 40 years for BRCA1 and by age 45 years for BRCA2 mutation carriers) to prevent ovarian and fallopian cancer, although there is a small residual risk of peritoneal cancer. The question of whether a concomitant hysterectomy should be performed is not yet resolved.

With this background information, Schrijver et al. posed the question of whether oral contraceptives affect the lifetime risk of developing cancer in BRCA mutation carriers. The authors used a simulation approach to estimate the absolute risks and benefits of combination oral contraceptive use on the cumulative incidence (and mortality) of breast, ovarian, and endometrial cancer combined. They created hypothetical cohorts of 10 000 women with a BRCA1 mutation and 10 000 women with a BRCA2 mutation and calculated the expected impact of oral contraceptives on absolute cancer incidence and mortality. They constructed 18 potential scenarios by altering key variables, including risk-reducing surgery, duration of oral contraceptive use, age at first use, and HRT use after oophorectomy. They assumed that the association between oral contraceptive use and risk of cancer among BRCA mutation carriers is similar to that observed in the general population. They applied BRCA-specific breast and ovarian cancer incidence rates but endometrial cancer rates from the Dutch population at large. Risk reduction with mastectomy and oophorectomy were set to 95% and 80% for breast and ovarian cancer, respectively.

They found that among women with both breasts and ovaries intact, oral contraceptive use was associated with a short-term increase in breast cancer incidence but a long-term decrease in ovarian cancer incidence (and endometrial cancer to a lesser extent). After age 40 years, the net benefit of oral contraceptives exceeded the net risk. This is not surprising given that the increased risk of breast cancer with oral contraceptives is transient, whereas the decrease in ovarian cancer risk is lifelong. Findings were similar for carriers of either gene mutation or when mortality was included as the endpoint.

There are various limitations to using a simulation approach. Notably, the hazard rates associated with the exposures were derived from the general population and not from BRCA mutation carriers specifically; furthermore, they may differ for women with a BRCA1 vs a BRCA2 mutation. There is a need for real data on oral contraceptives in cohorts of mutation carriers to confirm the observations of Schrijver et al.

The question remains: "Do oral contraceptives increase or decrease the lifetime risk of developing cancer in BRCA mutation carriers?" The answer is: "It depends." For a woman who elects for a preventive bilateral mastectomy, there is no downside to taking an oral contraceptive vis-à-vis her cancer risk. For a woman with both breasts intact and an oophorectomy, there is a net increase in her breast cancer risk—but does the size of the net increase in risk warrant consideration of an alternate form of contraception? Perhaps, but I think we would be better served if we were to rely on real data rather than modeled data, given the assumptions made.

This question is particularly important for a young woman who has just recently discovered she is carrying a BRCA1 or BRCA2 mutation and is considering oral contraceptives for the purpose of contraception. Her decision to take the pill or not is likely made well before she is a candidate for preventive surgery, and it may be unsettling to ask her to consider options

for preventive surgeries so well in advance. In some cases, young women may seek genetic testing for the sake of knowing if the pill is safe or is best avoided. Knowledge of the impact of contemporary modes of contraception, including injectable, implants, and intrauterine devices, will be important given their increasing popularity among women of reproductive age.
A second outcome in the study by Schrijver and colleagues is the impact of HRT use after oophorectomy on the incidence of breast cancer. These elevated risks are likely to be real given the well-described impact of progesterone signaling on mammary tumorigenesis as well as on breast cancer risk in women with a BRCA1 mutation. This represents a pressing concern given the need to manage symptoms attributed to early surgical menopause .
These are all important topics for discussion, and following the publication of the simulation study in this issue, these questions are sure to come up more frequently in sessions with genetic counselors and with other health-care providers.

Oral Contraceptive Use in BRCA1 and BRCA2 Mutation Carriers: Absolute Cancer Risks and Benefits. LH Schrijver, TM Mooij, A Pijpe, GS Sonke, M E Mourits, N Andrieu, AC Antoniou, DF Easton, C Engel, D Goldgar, EM John, K Kast, RL Milne, H Olsson, K-A Phillips, MB Terry, JL Hopper, FE van Leeuwen, MA Rookus. JNCI: Journal of the National Cancer Institute, Volume 114, Issue 4, April 2022, Pages 540–552, https://doi.org/10.1093/jnci/djac004https://academic.oup.com/jnci/article/114/4/540/6512064?login=true

Background To help *BRCA1* and *2* mutation carriers make informed decisions regarding use of combined-type oral contraceptive preparation (COCP), absolute risk-benefit estimates are needed for COCP-associated cancer.

Methods For a hypothetical cohort of 10 000 women, we calculated the increased or decreased cumulative incidence of COCP-associated (breast, ovarian, endometrial) cancer, examining 18 scenarios with differences in duration and timing of COCP use, uptake of prophylactic surgeries, and menopausal hormone therapy.

Results COCP use initially increased breast cancer risk and decreased ovarian and endometrial cancer risk long term. For 10 000 *BRCA1* mutation carriers, 10 years of COCP use from age 20 to 30 years resulted in 66 additional COCP-associated cancer cases by the age of 35 years, in addition to 625 cases expected for never users. By the age of 70 years such COCP use resulted in 907 fewer cancer cases than the expected 9093 cases in never users. Triple-negative breast cancer estimates resulted in 196 additional COCP-associated cases by age 40 years, in addition to the 1454 expected. For 10 000 *BRCA2* mutation carriers using COCP from age 20 to 30 years, 80 excess cancer cases were estimated by age 40 years in addition to 651 expected cases; by the age of 70 years, we calculated 382 fewer cases compared with the 6156 cases expected. The long-term benefit of COCP use diminished after risk-reducing bilateral salpingo-oophorectomy followed by menopausal hormone therapy use.

Conclusion Although COCP use in *BRCA1* and *BRCA2* mutation carriers initially increases breast, ovarian, and endometrial cancer risk, it strongly decreases lifetime cancer risk. Risk-reducing bilateral salpingo-oophorectomy and menopausal hormone therapy use appear to counteract the long-term COCP-benefit.

Obstetrical and Perinatal Outcomes in Female Survivors of Childhood and Adolescent Cancer: A Population-Based Cohort Study. A Zgardau, JG Ray, NN Baxter, C Nagamuthu, AL Park, S Gupta, PC Nathan. JNCI: Journal of the National Cancer Institute, Volume 114, Issue 4, April 2022, Pages 553–564, https://doi.org/10.1093/jnci/djac005 https://academic.oup.com/jnci/article/114/4/553/6511445?login=true

Background The likelihood of pregnancy and risk of obstetrical or perinatal complications is inadequately documented in female survivors of pediatric cancer.

Methods We assembled a population-based cohort of female survivors of cancer diagnosed at age 21 years and younger in Ontario, Canada, between 1985 and 2012. Survivors were matched 1:5 to women without prior cancer. Multivariable Cox proportional hazards and modified Poisson models assessed the likelihood of a recognized pregnancy and perinatal and maternal complications.

Results A total of 4062 survivors were matched to 20 308 comparisons. Median (interquartile range) age was 11 (4-15) years at cancer diagnosis and 25 (19-31) years at follow-up. By age 30 years, the cumulative incidence of achieving a recognized pregnancy was 22.3% (95% confidence interval [CI] = 20.7% to 23.9%) among survivors vs 26.6% (95% CI = 25.6% to 27.3%) among comparisons (hazard ratio = 0.80, 95% CI = 0.75 to 0.86). A lower likelihood of pregnancy was associated with a brain tumor, alkylator chemotherapy, cranial radiation, and hematopoietic stem cell transplantation. Pregnant survivors were as likely as cancer-free women to carry a pregnancy >20 weeks (relative risk [RR] = 1.01, 95% CI = 0.98 to 1.04). Survivors had a higher relative risk of severe maternal morbidity (RR = 2.31, 95% CI = 1.59 to 3.37), cardiac morbidity (RR = 4.18, 95% CI = 1.89 to 9.24), and preterm birth (RR = 1.57, 95% CI = 1.29 to 1.92). Preterm birth was more likely in survivors treated with hematopoietic stem cell transplantation (allogenic: RR = 8.37, 95% CI = 4.83 to 14.48; autologous: RR = 3.72, 95% CI = 1.66 to 8.35).

Conclusions Survivors of childhood or adolescent cancer are less likely to achieve a pregnancy and, once pregnant, are at higher risk for severe maternal morbidity and preterm birth.

Untangling the Relationship Between Clonal Hematopoiesis and Ovarian Cancer Therapies. K Takahashi. JNCI: Journal of the National Cancer Institute, Volume 114, Issue 4, April 2022, Pages 487–488, https://doi.org/10.1093/jnci/djab234 https://academic.oup.com/jnci/article/114/4/487/6486529?login=true

Historically, there is an unbreakable tie between clonal hematopoiesis (CH) and ovarian cancer. Mosaic *PPM1D* mutations in blood were first identified in patients with breast and ovarian cancers. It was believed that the mosaic *PPM1D* mutation in blood was a novel form of the genetic predisposition for breast and ovarian cancers. It was only later that we understood that this was a form of CH enriched in ovarian cancer patients exposed to chemotherapy treatment.

In this issue of the Journal, Weber-Lassalle and colleagues analyzed blood samples collected from patients with ovarian cancer enrolled in the AGO-TR1 observational trial. The study consisted of 448 patients with ovarian cancer whose germline *BRCA1* and *2* (g*BRCA1/2*) status was adjudicated. Covering 10 genes associated with CH (*ASXL1*, *DNMT3A*, *GNAS*, *JAK2*, *PPM1D*, *SF3B1*, *SH2B3*, *SRSF2*, *TET2*, and *TP53*), they detected CH in 17.6% of the patients. Not surprisingly, CH was associated with higher age at the blood draw and history of prior chemotherapy treatment. In addition, CH with *PPM1D* and *TP53* mutations was almost exclusively identified in patients who received at least one line of platinum-based chemotherapy. This is consistent with the preclinical findings that platinum chemotherapy promotes positive selection of CH with DNA damage pathway mutations, *PPM1D* and *TP53* .

One of the interesting hypotheses investigated in this study by Weber-Lassalle and colleagues was whether g*BRCA1/2* mutations alter the prevalence or patterns of CH. There is reason to believe that germline mutation might influence CH status. Prior studies have identified several germline variants associated with CH, such as *TERT*, *TET2*, and *CHEK2* . Therefore, the current study by Weber-Lasalle et al. offered an opportunity to investigate the relationship between g*BRCA1/2* and CH status.

Overall, there was no difference in the prevalence of CH between patients with g*BRCA1/2* mutations and patients without them in the study by Weber-Lasalle et al. Gene-specific analysis showed that *PPM1D* and *TP53* mutations correlated with g*BRCA1/2* status, as well as age and the number of prior platinum chemotherapy. However, the direct effect of g*BRCA1/2* status in the two CH mutations is unclear because g*BRCA1/2* status was also associated with an increased number of prior platinum therapy that could confound the association. Although the concept of g*BRCA1/2* mutations affecting CH development is tempting, the enrichment of *TP53*- and *PPM1D*-mutated CH in patients with g*BRCA1/2* mutations was likely driven by the increased exposures to chemotherapy in these patients. To investigate the direct relationship between g*BRCA1/2* status and CH, future study needs to analyze CH status before these patients are exposed to chemotherapy.

Current data still provides strong clinical evidence of the dose-dependent relationship between exposure to platinum chemotherapy and *PPM1D*- and *TP53*-mutated CH. Although none of the patients in the study by Weber-Lassalle and colleagues received therapy with poly (ADP-ribose) polymerase (PARP) inhibitors, a recent study found that PARP inhibitor therapy may promote the selection of *TP53*-mutated CH in ovarian cancer patients. These studies uncover the clonal mechanism of how different ovarian cancer therapies promote the development of CH and subsequently therapy-related myeloid neoplasms.

Clonal Hematopoiesis-Associated Gene Mutations in a Clinical Cohort of 448 Patients With Ovarian Cancer. Weber-Lassalle K, Ernst C, Reuss A, Möllenhoff K, Baumann K, Jackisch C, Hauke J, Dietrich D, Borde J, Park-Simon TW, Hanker L, Prieske K, Schmidt S, Weber-Lassalle N, Pohl-Rescigno E, Kommoss S, Marmé F, Heitz F, Stingl JC, Schmutzler RK, Harter P, Hahnen E. J Natl Cancer Inst. 2022 Apr 11;114(4):565-570. doi: 10.1093/jnci/djab231. PMID: 34963005; PMCID: PMC9002281. https://academic.oup.com/jnci/article-abstract/114/4/565/6486427?redirectedFrom=fulltext&login=true

Background: Cancer patients are at risk of secondary therapy-related myeloid neoplasms (t-MNs). Acquired blood-specific mutations in clonal hematopoiesis (CH)-associated genes are t-MN risk factors, and their occurrence associated with cancer therapy and age. Patients with ovarian cancer (OC) showed a particularly high prevalence of CH-associated gene mutations, which may additionally be explained by the high proportion of a hereditary disease cause in this cancer entity.

Methods: We performed a retrospective analysis of 448 OC patients enrolled in the AGO-TR1 study; 249 were enrolled at primary diagnosis and 199 at platinum-sensitive recurrence. Analyses included the most frequently altered CH-associated genes (ASXL1, DNMT3A, GNAS, JAK2, PPM1D, SF3B1, SH2B3, SRSF2, TET2, TP53). Results were analyzed according to the BRCA1/2 germline (gBRCA1/2) mutation status. All statistical tests were 2-sided.

Results: Advanced age at blood draw and a high number of prior platinum-based chemotherapy lines were risk factors to acquire CH-associated gene mutations, with gene-specific effects observed. Binomial logistic regression suggested increased probabilities for gBRCA1/2 mutation carriers to acquire CH-associated PPM1D and TP53 gene mutations (PPM1D: odds ratio = 4.30, 95% confidence interval = 1.48 to 12.46, P = .007; TP53: odds ratio = 6.20, 95% confidence interval = 0.98 to 53.9, P = .06). This observation was due to a statistically significantly increased number of platinum-based chemotherapy lines in gBRCA1/2 mutation carriers vs noncarriers (PPM1D: mean [SD] = 2.04 [1.27] vs 1.04 [0.99], P < .001; TP53: mean [SD] = 2.83 [1.33] vs 1.07 [1.01], P < .001). No interaction between platinum-based chemotherapy and gBRCA1/2 mutation status with the occurrence of CH-associated gene mutations was observed.

Conclusions: A positive gBRCA1/2 mutation status is not a risk factor to acquire CH-associated gene mutations. OC patients may benefit from monitoring CH-associated gene mutations, especially following carboplatin exposure. Future clinical studies are required to assess whether treatment regimen should be adapted according to individual t-MN risks.

Association of Pathogenic Variants in Hereditary Cancer Genes With Multiple Diseases. C Zeng, LA Bastarache, R Tao, E Venner, S Hebbring, JD Andujar, ST Bland, DR Crosslin, S Pratap, A Cooley, JA Pacheco, KD Christensen, E Perez, CLB Zawatsky, L Witkowski, H Zouk, C Weng, KA Leppig, PMA Sleiman, H Hakonarson, MS Williams, Y Luo, GP Jarvik, RC Green, WK Chung, AG Gharavi, NJ Lennon, HL Rehm, RA Gibbs, JF Peterson, DM Roden, GL Wiesner, JC Denny. JAMA Oncol. Published online April 21, 2022. doi:10.1001/jamaoncol.2022.0373 https://jamanetwork.com/journals/jamaoncology/article-abstract/2791551

Key Points

Question What is the range of conditions associated with hereditary cancer genes?

Findings This phenome-wide association study used genetic and phenotypic data derived from health-related data from electronic health records in 3 cohorts comprising 214 020 participants to identify 19 new diseases and conditions associated with pathogenic variants in 13 hereditary cancer genes. These new phenotypes included both neoplastic and nonneoplastic diseases.

Meaning These findings contribute to recognition and understanding of the full clinical spectrum of hereditary cancer syndromes, which can facilitate early detection of cancers and better management.

Abstract

Importance Knowledge about the spectrum of diseases associated with hereditary cancer syndromes may improve disease diagnosis and management for patients and help to identify high-risk individuals.

Objective To identify phenotypes associated with hereditary cancer genes through a phenome-wide association study.

Design, Setting, and Participants This phenome-wide association study used health data from participants in 3 cohorts. The Electronic Medical Records and Genomics Sequencing (eMERGEseq) data set recruited predominantly healthy individuals from 10 US medical centers from July 16, 2016, through February 18, 2018, with a mean follow-up through electronic health records (EHRs) of 12.7 (7.4) years. The UK Biobank (UKB) cohort recruited participants from March 15, 2006, through August 1, 2010, with a mean (SD) follow-up of 12.4 (1.0) years. The Hereditary Cancer Registry (HCR) recruited patients undergoing clinical genetic testing at Vanderbilt University Medical Center from May 1, 2012, through December 31, 2019, with a mean (SD) follow-up through EHRs of 8.8 (6.5) years.

Exposures Germline variants in 23 hereditary cancer genes. Pathogenic and likely pathogenic variants for each gene were aggregated for association analyses.

Main Outcomes and Measures Phenotypes in the eMERGEseq and HCR cohorts were derived from the linked EHRs. Phenotypes in UKB were from multiple sources of health-related data.

Results A total of 214 020 participants were identified, including 23 544 in eMERGEseq cohort (mean [SD] age, 47.8 [23.7] years; 12 611 women [53.6%]), 187 234 in the UKB cohort (mean [SD] age, 56.7 [8.1] years; 104 055 [55.6%] women), and 3242 in the HCR cohort (mean [SD] age, 52.5 [15.5] years; 2851 [87.9%] women). All 38 established gene-cancer associations were replicated, and 19 new associations were identified. These included the following 7 associations with neoplasms: *CHEK2* with leukemia (odds ratio [OR], 3.81 [95% CI, 2.64-5.48]) and plasma cell neoplasms (OR, 3.12 [95% CI, 1.84-5.28]), *ATM* with gastric cancer (OR, 4.27 [95% CI, 2.35-7.44]) and pancreatic cancer (OR, 4.44 [95% CI, 2.66-7.40]), *MUTYH* (biallelic) with kidney cancer (OR, 32.28 [95% CI, 6.40-162.73]), *MSH6* with bladder cancer (OR, 5.63 [95% CI, 2.75-11.49]), and *APC* with benign liver/intrahepatic bile duct tumors (OR, 52.01 [95% CI, 14.29-189.29]). The remaining 12 associations with nonneoplastic diseases included *BRCA1/2* with ovarian cysts (OR, 3.15 [95% CI, 2.22-4.46] and 3.12 [95% CI, 2.36-4.12], respectively), *MEN1* with acute pancreatitis (OR, 33.45 [95% CI, 9.25-121.02]), *APC* with gastritis and duodenitis (OR, 4.66 [95% CI, 2.61-8.33]), and *PTEN* with chronic gastritis (OR, 15.68 [95% CI, 6.01-40.92]).

Conclusions and Relevance The findings of this genetic association study analyzing the EHRs of 3 large cohorts suggest that these new phenotypes associated with hereditary cancer genes may facilitate early detection and better management of cancers. This study highlights the potential benefits of using EHR data in genomic medicine.

Quality-of-Life Outcomes and Toxic Effects Among Patients With Cancers of the Uterus Treated With Stereotactic Pelvic Adjuvant Radiation Therapy: The SPARTACUS Phase 1/2 Nonrandomized Controlled Trial. E Leung, AP Gladwish, M Davidson, A Taggar, V Velker, E Barnes, L Mendez, E Donovan, LT Gien, A Covens, D Vicus, R Kupets, H MacKay, K Han, P Cheung, L Zhang, A Loblaw, DP D'Souza. JAMA Oncol. Published online April 14, 2022. doi:10.1001/jamaoncol.2022.0362 https://jamanetwork.com/journals/jamaoncology/article-abstract/2791270

Importance Adjuvant radiation plays an important role in reducing locoregional recurrence in patients with uterine cancer. Although hypofractionated radiotherapy may benefit health care systems and the global community while decreasing treatment burden for patients traveling for daily radiotherapy, it has not been studied prospectively nor in randomized trials for treatment of uterine cancers, and the associated toxic effects and patient quality of life are unknown.

Objective To evaluate acute genitourinary and bowel toxic effects and patient-reported outcomes following stereotactic hypofractionated adjuvant radiation to the pelvis for treatment of uterine cancer.

Design, Setting, and Participants The Stereotactic Pelvic Adjuvant Radiation Therapy in Cancers of the Uterus (SPARTACUS) phase 1/2 nonrandomized controlled trial of patients accrued between May 2019 and August 2021 was

conducted as a multicenter trial at 2 cancer centers in Ontario, Canada. In total, 61 patients with uterine cancer stages I through III after surgery entered the study.
Interventions Stereotactic adjuvant pelvic radiation to a dose of 30 Gy in 5 fractions administered every other day or once weekly.
Main Outcomes and Measures Assessments of toxic effects and patient-reported quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires C30 and endometrial EN24) were collected at baseline, fractions 3 and 5, and at 6 weeks and 3 months of follow-up. Descriptive analysis was conducted, calculating means, SDs, medians, IQRs, and ranges for continuous variables and proportions for categorical variables. Univariate generalized linear mixed models were generated for repeated measurements on the quality-of-life scales.
Results A total of 61 patients were enrolled (median age, 66 years; range, 51-88 years). Tumor histologic results included 39 endometrioid adenocarcinoma, 15 serous or clear cell, 3 carcinosarcoma, and 4 dedifferentiated. Sixteen patients received sequential chemotherapy, and 9 received additional vault brachytherapy. Median follow-up was 9 months (IQR, 3-15 months). Of 61 patients, worst acute gastrointestinal tract toxic effects of grade 1 were observed in 33 patients (54%) and of grade 2 in 8 patients (13%). For genitourinary worst toxic effects, grade 1 was observed in 25 patients (41%) and grade 2 in 2 patients (3%). One patient (1.6%) had an acute grade 3 gastrointestinal tract toxic effect of diarrhea at fraction 5 that resolved at follow-up. Only patient-reported diarrhea scores were both clinically (scores ≥10) and statistically significantly worse at fraction 5 (mean [SD] score, 35.76 [26.34]) compared with baseline (mean [SD] score, 6.56 [13.36]; $P < .001$), but this symptom improved at follow-up.
Conclusions and Relevance Results of this phase 1/2 nonrandomized controlled trial suggest that stereotactic hypofractionated radiation was well tolerated at short-term follow-up for treatment of uterine cancer. Longer follow-up and future randomized studies are needed to further evaluate this treatment.

Are We Finally Ready for the Widespread Adoption of Stereotactic Radiation in Gynecologic Cancers? Williams VM, Balogun O, Alektiar K. JAMA Oncol. Published online April 14, 2022. doi:10.1001/jamaoncol.2022.0260 https://jamanetwork.com/journals/jamaoncology/article-abstract/2791273?widget=personalizedcontent&previousarticle=2767675
In this issue of JAMA Oncology, Leung et al1 present the first prospective phase 1/2 single-group trial, The Stereotactic Pevlic Adjuvant Radiation Therapy in Cancers of the Uterus (SPARTACUS), of accelerated hypofractionation/stereotactic body radiation therapy (SBRT) for postoperative pelvic radiation in patients with stage I to III uterine cancer. In total, 61 patients were accrued between May 2019 and August 2021 and received 30 Gy in 5 fractions, using either once a week (13 patients) or every other day (48 patients) treatment schedules. The primary end point was physician-reported acute gastrointestinal (GI) tract and genitourinary toxic effects. There are many potential benefits to a shorter radiation treatment schedule, as the authors discuss. The benefits include quicker time of completing systemic therapy in advanced uterine cancer, decreased financial challenges owing to travel, lost wages, and housing that may be needed to facilitate weeks of treatment, and decreased exposure to high-risk hospital settings during the height of the COVID-19 pandemic. The authors found at a median follow-up of 9 months (IQR, 3-15 months) that rates of acute GI tract toxic effects of grade 1 and 2 were 54% and 13%, respectively, and acute genitourinary toxic effects of grade 1 and 2 were 41% and 3%, respectively. Treatment with stereotactic radiation would have been deemed too toxic if more than 20% of patients had grade 3 or higher toxic effects.

Adherence to National Guidelines on Cervical Screening: A Population-Based Evaluation from a Statewide Registry. Castle PE, Kinney WK, Chen L, Kim JJ, Jenison S, Rossi G, Kang H, Cuzick J, Wheeler CM; New Mexico HPV Pap Registry Steering Committee. J Natl Cancer Inst. 2021 Aug 31;114(4):626–30. doi: 10.1093/jnci/djab173. Epub ahead of print. PMID: 34463763; PMCID: PMC9002271. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9002271/
In 2012, national recommendations for cervical cancer screening of women aged 30-64 years were quinquennial human papillomavirus and cytology cotesting or triennial cytology. Data from a statewide surveillance program in New Mexico demonstrated 65.2% (95% confidence interval [95% CI] = 64.6% to 65.7%) of women screened in 2019 had a negative cotest within the last 3 years. Percentages of women screened in 2013, 2016, and 2019 with a prior negative cotest more than 5 years and up to 7 years ago were 2.6% (95% CI = 2.2% to 2.9%), 2.1% (95% CI = 1.9% to 2.2%), and 6.5% (95% CI = 6.2% to 6.8%), respectively (2-sided Ptrend < .001). Percentages of women screened in 2013, 2016, and 2019 with a prior negative cytology more than 5 years and up to 7 years ago were 3.8% (95% CI = 3.7% to 3.9%), 9.0% (95% CI = 8.7% to 9.3%), and 14.9% (95% CI = 14.4% to 15.4%), respectively (2-sided Ptrend < .001). Thus, in 2019, only 12.7% (95% CI = 12.4% to 13.1%) of the 30 215 women aged 30-64 years underwent cotesting and 27.7% (95% CI = 27.1% to 28.3%) of the 18 733 underwent cytology at the recommended interval. The observed under- and overscreening could result in increases in cervical cancer incidence and harms and costs, respectively.

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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).