In The Know

Gyn Onc Literature of Significance

Ed's List

September 2021- August 2021

Online at https://igcs.org/in-the-know/

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

September

Distinct transcriptional programs stratify ovarian cancer cell lines into the five major histological subtypes. Bethany M. Barnes, Louisa Nelson, Anthony Tighe, George J. Burghel, I-Hsuan Lin, Sudha Desai, Joanne C. McGrail, Robert D. Morgan & Stephen S. TaylorGenome Med 13, 140 (2021). https://doi.org/10.1186/s13073-021-00952-5 https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-021-00952-5

Background Epithelial ovarian cancer (OC) is a heterogenous disease consisting of five major histologically distinct subtypes: high-grade serous (HGSOC), low-grade serous (LGSOC), endometrioid (ENOC), clear cell (CCOC) and mucinous (MOC). Although HGSOC is the most prevalent subtype, representing 70–80% of cases, a 2013 landmark study by Domcke et al. found that the most frequently used OC cell lines are not molecularly representative of this subtype. This raises the question, if not HGSOC, from which subtype do these cell lines derive? Indeed, non-HGSOC subtypes often respond poorly to chemotherapy; therefore, representative models are imperative for developing new targeted therapeutics.
Methods Non-negative matrix factorisation (NMF) was applied to transcriptomic data from 44 OC cell lines in the Cancer Cell Line Encyclopedia, assessing the quality of clustering into 2–10 groups. Epithelial OC subtypes were assigned to cell lines optimally clustered into five transcriptionally distinct classes, confirmed by integration with subtype-specific mutations. A transcriptional subtype classifier was then developed by trialling three machine learning algorithms using subtype-specific metagenes defined by NMF. The ability of classifiers to predict subtype was tested using RNA sequencing of a living biobank of patient-derived OC models.
Results Application of NMF optimally clustered the 44 cell lines into five transcriptionally distinct groups. Close inspection of orthogonal datasets revealed this five-cluster delineation corresponds to the five major OC subtypes. This NMF-based classification validates the Domcke et al. analysis, in identifying lines most representative of HGSOC, and additionally identifies models representing the four other subtypes. However, NMF of the cell lines into two clusters did not align with the dualistic model of OC and suggests this classification is an oversimplification. Subtype designation of patient-derived models by a random forest transcriptional classifier aligned with prior diagnosis in 76% of unambiguous cases. In cases where there was disagreement, this often indicated potential alternative diagnosis, supported by a review of histological, molecular and clinical features.
Conclusions This robust classification informs the selection of the most appropriate models for all five histotypes. Following further refinement on larger training cohorts, the transcriptional classification may represent a useful tool to support the classification of new model systems of OC subtypes.

A machine learning approach to identify predictive molecular markers for cisplatin chemosensitivity following surgical resection in ovarian cancer. NB Shannon, LLY Tan, QX Tan, JW-S Tan, J Hendrikson, WH Ng, G Ng, Y Liu, X-YS Ong, R Nadarajah, JSM Wong, GHC Tan, KC Soo, MC Ching Teo, CS Chia, C-AJ. Ong Sci Rep 11, 16829 (2021). https://doi.org/10.1038/s41598-021-96072-6 https://www.nature.com/articles/s41598-021-96072-6

Ovarian cancer is associated with poor prognosis. Platinum resistance contributes significantly to the high rate of tumour recurrence. We aimed to identify a set of molecular markers for predicting platinum sensitivity. A signature predicting cisplatin sensitivity was generated using the Genomics of Drug Sensitivity in Cancer and The Cancer Genome Atlas databases. Four potential biomarkers (CYTH3, GALNT3, S100A14, and ERI1) were identified and optimized for

immunohistochemistry (IHC). Validation was performed on a cohort of patients (n = 50) treated with surgical resection followed by adjuvant carboplatin. Predictive models were established to predict chemosensitivity. The four biomarkers were also assessed for their ability to prognosticate overall survival in three ovarian cancer microarray expression datasets from The Gene Expression Omnibus. The extreme gradient boosting (XGBoost) algorithm was selected for the final model to validate the accuracy in an independent validation dataset (n = 10). CYTH3 and S100A14, followed by nodal stage, were the features with the greatest importance. The four gene signature had comparable prognostication as clinical information for two-year survival. Assessment of tumour biology by means of gene expression can serve as an adjunct for prediction of chemosensitivity and prognostication. Potentially, the assessment of molecular markers alongside clinical information offers a chance to further optimize therapeutic decision making.

Impact of the Time Interval Between Primary Debulking Surgery and Start of Adjuvant Chemotherapy in Advanced Epithelial Ovarian Cancer. H Lin, WH Chen, CH Wu, YC Ou, YJ Chen, YY Chen, YH Lin, HC Fu. Cancer Manag Res. 2021;13:5413-5422 https://doi.org/10.2147/CMAR.S313013 https://www.dovepress.com/impact-of-the-time-interval-between-primary-debulking-surgery-and-star-peer-reviewed-fulltext-article-CMAR

Aim: To investigate whether the time interval between primary debulking surgery (PDS) and initiating adjuvant chemotherapy affects survival in patients with epithelial ovarian cancer (EOC).

Methods: We retrospectively reviewed FIGO stage IIB to IV EOC patients who received PDS followed by adjuvant chemotherapy in our hospital between January 2008 and December 2016. The optimal cut-off time interval to chemotherapy related to survival was determined using the Contal and O'Quigley method and Cox hazard models. Cox regression analysis was used to identify the independent effect of time interval on survival.

Results: A total of 152 patients were identified and divided into three groups based on the time interval between PDS and initiating adjuvant chemotherapy: early (< 23 days), intermediate (23– 43 days) and late (> 43 days). The intermediate group had a significantly better median progression-free survival (PFS, 35.5 months) compared to the early (20 months) and late (22.6 months) groups. After adjustments for confounding factors, time interval was still an independent variable affecting PFS. The intermediate group was associated with a better PFS compared with the early and late groups (hazard ratio 0.27, 95% CI 0.10– 0.83, p=0.002). There was no statistical significance in overall survival (OS) in univariate or multivariate analysis, although there was a trend towards better OS in the intermediate group.

Conclusion: Our results provide evidence that the time interval from PDS to chemotherapy influences PFS in patients with advanced EOC. The optimal time to initiate chemotherapy was between 23 and 43 days, within 3– 6 weeks post-operatively. Initiating chemotherapy early (< 23 days) did not appear to benefit PFS.

Cost-effectiveness Analysis of Genotype-Specific Surveillance and Preventive Strategies for Gynecologic Cancers Among Women With Lynch Syndrome. JD Wright, ER Silver, SX Tan, C Hur, F Kastrinos. JAMA Netw Open. 2021;4(9):e2123616. doi:10.1001/jamanetworkopen.2021.23616 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2784029?guestAccessKey=99f1e377-1262-4eb4-a71a-d3bd2fbedb10&utm_source=silverchair&utm_campaign=jama_network&utm_content=onc_weekly_highlights&cmp=1&utm_medium=email

Key Points

Question What are the most cost-effective gene-specific screening and preventive strategies for reducing gynecologic cancer risk for women with Lynch syndrome (LS)?

Findings This cost-effectiveness economic evaluation found that optimal screening strategies varied by genotype. A novel 2-stage approach with hysterectomy and bilateral salpingectomy at age 40 years and delayed oophorectomy at age 50 years was effective and cost-effective for individuals with *MLH1* and *MSH6* genetic variants, while hysterectomy with bilateral salpingo-oophorectomy was optimal at age 40 years for individuals with *MSH2* genetic variants and at age 50 years for individuals with *PMS2* variants.

Meaning These findings suggest that surgical decision-making should consider LS genotype for gynecologic cancer prevention and that a novel 2-stage approach may be associated with decreased cancer risk while avoiding early menopause in individuals with select genetic variants.

Abstract

Importance With the expansion of multigene testing for cancer susceptibility, Lynch syndrome (LS) has become more readily identified among women. The condition is caused by germline pathogenic variants in DNA mismatch repair genes (ie, *MLH1, MSH2, MSH6*, and *PMS2*) and is associated with high but variable risks of endometrial and ovarian cancers based on genotype. However, current guidelines on preventive strategies are not specific to genotypes.

Objective To assess the cost-effectiveness of genotype-specific surveillance and preventive strategies for LS-associated gynecologic cancers, including a novel, risk-reducing surgical approach associated with decreased early surgically induced menopause.

Design, Setting, and Participants This economic evaluation developed a cohort-level Markov simulation model of the natural history of LS-associated gynecologic cancer for each gene, among women from ages 25 to 75 years or until death

from a health care perspective. Age was varied at hysterectomy and bilateral salpingo-oophorectomy (hyst-BSO) and at surveillance initiation, and a 2-stage surgical approach (ie, hysterectomy and salpingectomy at age 40 years and delayed oophorectomy at age 50 years [hyst-BS]) was included. Extensive 1-way and probabilistic sensitivity analyses were performed.

Interventions Hyst-BSO at ages 35 years, 40 years, or 50 years with or without annual surveillance beginning at age 30 years or 35 years or hyst-BS at age 40 years with oophorectomy delayed until age 50 years.

Main Outcomes and Measures Incremental cost-effectiveness ratio (ICER) between management strategies within an efficiency frontier.

Results For women with *MLH1* and *MSH6* variants, the optimal strategy was the 2-stage approach, with respective ICERs of $33 269 and $20 008 compared with hyst-BSO at age 40 years. Despite being cost-effective, the 2-stage approach was associated with increased cancer incidence and mortality compared with hyst-BSO at age 40 years for individuals with *MLH1* variants (incidence: 7.76% vs 3.84%; mortality: 5.74% vs 2.55%) and those with *MSH6* variants (incidence: 7.24% vs 4.52%; mortality: 5.22% vs 2.97%). Hyst-BSO at age 40 years was optimal for individuals with *MSH2* variants, with an ICER of $5180 compared with hyst-BSO at age 35 years, and was associated with 4.42% cancer incidence and 2.97% cancer mortality. For individuals with *PMS2* variants, hyst-BSO at age 50 years was optimal and all other strategies were dominated; hyst-BSO at age 50 years was associated with an estimated cancer incidence of 0.68% and cancer mortality of 0.29%.

Conclusions and Relevance These findings suggest that gene-specific preventive strategies for gynecologic cancers in LS may be warranted and support hyst-BSO at age 40 years for individuals with *MSH2* variants. For individuals with *MLH1* and *MSH6* variants, these findings suggest that a novel 2-stage surgical approach with delayed oophorectomy may be an alternative to hyst-BSO at age 40 years to avoid early menopause, and for individuals with *PMS2* variants, the findings suggest that hyst-BSO may be delayed until age 50 years.

Analysis of Launch and Postapproval Cancer Drug Pricing, Clinical Benefit, and Policy Implications in the US and Europe. KN. Vokinger, TJ Hwang, P Daniore, CWC. Lee, A Tibau, T Grischott, TJ Rosemann, AS Kesselheim. JAMA Oncol. 2021;7(9):e212026. doi:10.1001/jamaoncol.2021.2026 https://jamanetwork.com/journals/jamaoncology/article-abstract/2781390?guestAccessKey=74234454-47cd-41d8-bd6b-6bae907f211b&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamaoncology&utm_content=etoc&utm_term=091621

Key Points

Question Was there an association between clinical benefit, launch prices and postlaunch price changes for cancer drugs in the US compared with Europe (England, Germany, and Switzerland)?

Findings In this economic evaluation of the US compared with 3 European countries, launch prices of cancer drugs were higher in the US than in Europe; prices frequently increased faster than inflation in the US but decreased on inflation-adjusted terms in Europe. Launch prices and postlaunch price increases were not associated with clinical benefit in any country.

Meaning The findings of this study suggest that, although the US would need to take the most substantial steps to address the high costs of cancer drugs, Europe could also reexamine their pricing regulations to ensure better alignment with the clinical value.

Abstract

Importance The high cost of cancer medicines is a public health challenge. Policy makers in the US and Europe are debating reforms to drug pricing that would cover both the prices of new medicines when entering the market and price increases after they are launched.

Objective To assess launch prices, postlaunch price changes, and clinical benefit of cancer drugs in the US compared with 3 European countries (England, Germany, and Switzerland).

Design, Setting, and Participants This economic evaluation identified all new drugs that were approved for use in the US, England, Germany, and Switzerland with initial indications for treatment of adult solid tumor and hematologic cancers. Analysis included drugs approved by the US Food and Drug Administration between January 1, 2009, and December 31, 2019, and by the European Medicines Agency and Swissmedic until December 31, 2019. Prices were adjusted for currency and inflation. Clinical benefit of drugs indicated for solid tumors was assessed using the American Society of Clinical Oncology Value Framework and European Society for Medical Oncology Magnitude of Clinical Benefit Scale. Using Spearman rank correlation coefficients, correlations between clinical benefit and launch prices and postlaunch price changes for each country were evaluated.

Main Outcomes and Measures Launch prices, postlaunch price changes, and clinical benefit of cancer drugs.

Results The cohort included 65 drugs: 47 (72%) approved for solid tumors and 18 (28%) for hematologic cancers. In all countries, the lowest median monthly treatment costs at launch were greater in 2018-2019 vs 2009-2010: $14 580 vs $5790 in the US, $5888 vs $4289 in Germany, $6593 vs $5784 in Switzerland, and $6867 vs $3939 in England. Between 2009 and 2019, 48 of 65 (74%) cancer drugs had price increases in the US that were greater than inflation. Only 1 of 62 (2%) drugs in England, 0 of 60 drugs in Germany, and 7 of 56 drugs (13%) in Switzerland had a median price increase greater

than inflation. There were no associations between launch prices or postlaunch price changes and clinical benefit in any assessed country.

Conclusions and Relevance During this economic evaluation study period, launch prices of cancer drugs were substantially higher in the US than in the assessed similar high-income European countries, a gap that increased in the years after approval. Cancer drug prices frequently increased faster than inflation in the US but decreased on inflation-adjusted terms in Europe. Price changes were not associated with clinical benefit in any country.

Mapping genomic and epigenomic evolution in cancer ecosystems. T Ushijima, SJ Clark, P Tan. SCIENCE 2021 373, (6562) 1474-1479 DOI: 10.1126/science.abh1645 https://www.science.org/doi/10.1126/science.abh1645

Cancer is a major cause of global mortality underpinned by genomic and epigenomic derangements. Here, we highlight the importance of multimodal data integration in understanding the molecular evolution of malignant cell states across the cancer life cycle. The widespread presence of driver mutations and epigenetic alterations in normal-appearing tissues is prompting a reassessment of how cancer initiation is defined. In later-stage cancers, studying the roles of clonal selection, epigenomic adaptation, and persister cells in metastasis and therapy resistance is an emerging field. Finally, the importance of tumor ecosystems in driving cancer development is being unraveled by single-cell and spatial technologies at unprecedented resolution. Improving cancer risk assessment and accelerating therapeutic discovery for patients will require robust, comprehensive, and integrated temporal, spatial, and multilevel tumor atlases across the cancer life cycle.

Increased risk of second primary malignancies among endometrial cancer survivors receiving surgery alone: A population-based analysis. Y-L Lai, C-J Chiang, Y-L Chen,| S-L You, Y-Y Chen, Y-C Chiang, Y-J Tai, H-C Hsu, C-A Chen, W-F Cheng. Cancer Medicine Cancer Med. 2021;00:1–10. https://doi.org/10.1002/cam4.3861 https://onlinelibrary.wiley.com/doi/10.1002/cam4.3861

Background Women with endometrial cancer (EC) have favorable prognoses, leaving them vulnerable to the development of second primary cancers (SPCs). We investigated the SPC risk and survival outcomes among EC patients treated with surgery alone in order to exclude the impact of adjuvant treatment on the results.

Methods Data from the Taiwan Cancer Registry from 1995 to 2013 were analyzed. Standardized incidence ratios (SIRs) of SPCs among EC survivors were calculated.

Results Among 7725 women enrolled, 478 developed an SPC. The overall SIR for SPCs in EC survivors was 2.84 (95% confidence interval [CI] 2.59–3.10) compared with the general female population. Women diagnosed with EC at age <50 years had a higher SIR for an SPC than those diagnosed at age ≥50 years (SIR = 4.38 vs. 1.28). The most frequent site of an SPC was the small intestine (SIR = 8.39, 95% CI 2.72–19.58), followed by the kidney (SIR = 4.84, 95% CI 1.78–10.54), and oral cavity (SIR = 4.52, 95% CI 2.17–8.31). Women, regardless of age at EC diagnosis, had significantly higher SIRs for subsequent breast, colorectal, lung, and thyroid cancer, and lymphoma. Women with an SPC had shorter overall survival than those without (5-year: 88.9 vs. 94.2%, 10-year: 71.3 vs. 89.8%, 15-year: 62.3 vs. 86.1%, and 20-year: 47.6 vs. 81.1%, all ps<0.001).

Conclusions Even women treated for EC with surgery alone, especially young EC survivors, had an increased risk of SPCs. Genetic counseling/testing is recommended for young EC patients, and all are recommended to receive regular surveillance and screening for breast, colorectal, and lung cancers.

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. Published online September 30, 2021. doi:10.1001/jamaoncol.2021.4252 https://jamanetwork.com/journals/jamaoncology/fullarticle/2784404?guestAccessKey=5358a4f8-d712-470d-b931-148e2e7cb43d&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamaoncology&utm_content=olf&utm_term=093021

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.

Clinical and pathological associations of PTEN expression in ovarian cancer: a multicentre study from the Ovarian Tumour Tissue Analysis Consortium

. FC Martins, DL Couturier, A Paterson, et al. Br J Cancer 123, 793–802 (2020). https://doi.org/10.1038/s41416-020-0900-0 https://www.nature.com/articles/s41416-020-0900-0.pdf

Background PTEN loss is a putative driver in histotypes of ovarian cancer (high-grade serous (HGSOC), endometrioid (ENOC), clear cell (CCOC), mucinous (MOC), low-grade serous (LGSOC)). We aimed to characterise PTEN expression as a biomarker in epithelial ovarian cancer in a large population-based study.

Methods Tumours from 5400 patients from a multicentre observational, prospective cohort study of the Ovarian Tumour Tissue Analysis Consortium were used to evaluate associations between immunohistochemical PTEN patterns and overall survival time, age, stage, grade, residual tumour, CD8+ tumour-infiltrating lymphocytes (TIL) counts, expression of oestrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR) by means of Cox proportional hazard models and generalised Cochran–Mantel–Haenszel tests.

Results Downregulation of cytoplasmic PTEN expression was most frequent in ENOC (most frequently in younger patients; p value = 0.0001) and CCOC and was associated with longer overall survival in HGSOC (hazard ratio: 0.78, 95% CI: 0.65–0.94, p value = 0.022). PTEN expression was associated with ER, PR and AR expression (p values: 0.0008, 0.062 and 0.0002, respectively) in HGSOC and with lower CD8 counts in CCOC (p value < 0.0001). Heterogeneous expression of PTEN was more prevalent in advanced HGSOC (p value = 0.019) and associated with higher CD8 counts (p value = 0.0016).

Conclusions PTEN loss is a frequent driver in ovarian carcinoma associating distinctly with expression of hormonal receptors and CD8+ TIL counts in HGSOC and CCOC histotypes.

Matched-pair Analysis for Survival Endpoints Between Women With Early-stage Uterine Carcinosarcoma and Uterine Serous Carcinoma J Yahya, S Zhu, C Burmeister, MY Hijaz, MA Elshaikh. American Journal of Clinical Oncology: September 2021 - Volume 44 - Issue 9 - p 463-468 doi: 10.1097/COC.0000000000000851 https://journals.lww.com/amjclinicaloncology/Fulltext/2021/09000/Matched_pair_Analysis_for_Survival_Endpoints.4.aspx

Objective: The objective of this study was to compare survival endpoints between women with uterine carcinosarcoma and those with uterine serous carcinoma utilizing matching analysis.

Methods: Patients with stages I to II who underwent hysterectomy at our institution were included in this analysis. Patients with carcinosarcoma were then matched to patients with serous carcinoma based on stage, and adjuvant management received (observation, radiation treatment alone, chemotherapy alone, or combined modality with radiotherapy and chemotherapy. Recurrence-free survival, disease-specific survival, and overall survival were calculated for the 2 groups.
Results: A total of 134 women were included (67 women with carcinosarcoma and 67 with serous carcinoma, matched 1:1). There was no statistically significant difference between the 2 groups regarding 5-year recurrence-free survival (59% vs. 62%), disease-specific survival (66% vs. 67%), or overall survival (53% vs. 57%), respectively. The only independent predictor of shorter recurrence-free survival for the entire cohort was the lack of adjuvant combined modality therapy, while lower uterine segment involvement was the only independent predictor for shorter disease-specific survival. Lack of lymph node dissection and lack of adjuvant combined modality therapy were independent predictors of shorter overall survival.
Discussion: When matched based on stage and adjuvant treatment, our study suggests that there is no statistically significant difference in survival endpoints between women with early-stage carcinosarcoma and serous carcinoma. Adjuvant combined modality treatment is an independent predictor of longer recurrence-free survival and overall survival.

Acquired RAD51C Promoter Methylation Loss Causes PARP Inhibitor Resistance in High-Grade Serous Ovarian Carcinoma. K Nesic, O Kondrashova, RM Hurley, CD McGehee, CJ Vandenberg, G-Y Ho, E Lieschke, G Dall, N Bound, K Shield-Artin, M Radke, A Musafer, ZQ Chai, MRE Ghamsari, MI Harrell, D Kee, I Olesen, O McNally, N Traficante, Australian Ovarian Cancer Study, A DeFazio, DDL Bowtell, EM Swisher, SJ Weroha, K Nones, N Waddell, SH Kaufmann, A Dobrovic, MJ Wakefield, CL Scott
Cancer Res September 15 2021 (81) (18) 4709-4722; DOI: 10.1158/0008-5472.CAN-21-0774 https://cancerres.aacrjournals.org/content/81/18/4709
In high-grade serous ovarian carcinoma (HGSC), deleterious mutations in DNA repair gene *RAD51C* are established drivers of defective homologous recombination and are emerging biomarkers of PARP inhibitor (PARPi) sensitivity. *RAD51C* promoter methylation (me*RAD51C*) is detected at similar frequencies to mutations, yet its effects on PARPi responses remain unresolved.
In this study, three HGSC patient-derived xenograft (PDX) models with methylation at most or all examined CpG sites in the *RAD51C* promoter show responses to PARPi. Both complete and heterogeneous methylation patterns were associated with *RAD51C* gene silencing and homologous recombination deficiency (HRD). PDX models lost me*RAD51C* following treatment with PARPi rucaparib or niraparib, where a single unmethylated copy of *RAD51C* was sufficient to drive PARPi resistance. Genomic copy number profiling of one of the PDX models using SNP arrays revealed that this resistance was acquired independently in two genetically distinct lineages.
In a cohort of 12 patients with *RAD51C*-methylated HGSC, various patterns of me*RAD51C* were associated with genomic "scarring," indicative of HRD history, but exhibited no clear correlations with clinical outcome. Differences in methylation stability under treatment pressure were also observed between patients, where one HGSC was found to maintain me*RAD51C* after six lines of therapy (four platinum-based), whereas another HGSC sample was found to have heterozygous me*RAD51C* and elevated *RAD51C* gene expression (relative to homozygous me*RAD51C* controls) after only neoadjuvant chemotherapy.
As me*RAD51C* loss in a single gene copy was sufficient to cause PARPi resistance in PDX, methylation zygosity should be carefully assessed in previously treated patients when considering PARPi therapy.
Significance: Homozygous *RAD51C* methylation is a positive predictive biomarker for sensitivity to PARP inhibitors, whereas a single unmethylated gene copy is sufficient to confer resistance.

Development of a Novel Mouse Model of Spontaneous High-Risk HPVE6/E7–Expressing Carcinoma in the Cervicovaginal Tract. TR Henkle, B Lam, YJ Kung, J Lin, S-H Tseng, L Ferrall, D Xing, C-F Hung and T-C Wu. Cancer Res September 1 2021 (81) (17) 4560-4569; DOI: 10.1158/0008-5472.CAN-21-0399 https://cancerres.aacrjournals.org/content/81/17/4560
Current preclinical models for cervical cancer lack important clinical and pathologic features. To improve upon these models, we aimed to develop a novel, spontaneous HPV16-expressing carcinoma model that captures major aspects of HPV-associated cancer in the female genital tract. This novel preclinical model features (i) expression of HPV oncogenes E6 and E7 in the tumors in female reproductive tract of mice, (ii) spontaneous progression through high-grade squamous intraepithelial lesion (HSIL) to carcinoma, and (iii) flexibility to model cancers from different high-risk HPV genotypes. This was accomplished by injecting plasmids expressing HPV16 E6/E7-luciferase, AKT, c-myc, and Sleeping Beauty transposase into the cervicovaginal tract of C57BL/6 mice followed by electroporation. Cell lines derived from these tumors expressed HPV16 E6/E7 oncogenes, formed tumors in immunocompetent mice, and displayed carcinoma morphology. In all, this novel HPV-associated cervicogenital carcinoma model and HPV16E6/E7–expressing tumor cell line improves upon current HPV16-E6/E7–expressing tumor models. These tumor models may serve as important preclinical models for the development of therapeutic HPV vaccines or novel therapeutic interventions against HPV E6/E7–expressing tumors.
Significance: This study describes the development of a clinically relevant mouse model of cervicovaginal carcinoma that progresses from high-grade lesions and recapitulates key features of human HPV$^+$ cervical cancer.

Maximizing cancer prevention through genetic navigation for Lynch syndrome detection in women with newly diagnosed endometrial and nonserous/nonmucinous epithelial ovarian cancer. SR Kim, A Tone, RH Kim, M Cesari, BA Clarke, L Eiriksson, TL Hart, M Aronson, S Holter, A Lytwyn, M Maganti, L Oldfield, St Gallinger, MQ Bernardini, AM Oza, B Djordjevic, J Lerner-Ellis, E Van de Laar, D Vicus, TJ Pugh, A Pollett, SE Ferguson. Cancer. 2021. https://doi.org/10.1002/cncr.33625

Background Despite recommendations for reflex immunohistochemistry (IHC) for mismatch repair (MMR) proteins to identify Lynch syndrome (LS), the uptake of genetic assessment by those who meet referral criteria is low. The authors implemented a comprehensive genetic navigation program to increase the uptake of genetic testing for LS in patients with endometrial cancer (EC) or nonserous/nonmucinous ovarian cancer (OC).

Methods Participants with newly diagnosed EC or OC were prospectively recruited from 3 cancer centers in Ontario, Canada. Family history questionnaires were used to assess LS-specific family history. Reflex IHC for MMR proteins was performed with the inclusion of clinical directives in pathology reports. A trained genetic navigator initiated a genetic referral on behalf of the treating physician and facilitated genetic referrals to the closest genetics center.

Results A total of 841 participants (642 with EC, 172 with OC, and 27 with synchronous EC/OC) consented to the study; 194 (23%) were MMR-deficient by IHC. Overall, 170 women (20%) were eligible for a genetic assessment for LS: 35 on the basis of their family history alone, 24 on the basis of their family history and IHC, 82 on the basis of IHC alone, and 29 on the basis of clinical discretion. After adjustments for participants who died (n = 6), 149 of 164 patients (91%) completed a genetic assessment, and 111 were offered and completed genetic testing. Thirty-four women (4.0% of the total cohort and 30.6% of those with genetic testing) were diagnosed with LS: 5 with mutL homolog 1 (MLH1), 9 with mutS homolog 2 (MSH2), 15 with mutS homolog 6 (MSH6), and 5 with PMS2.

Conclusions The introduction of a navigated genetic program resulted in a high rate of genetic assessment (>90%) in patients with gynecologic cancer at risk for LS.

BRCA1/2 and Endometrial Cancer Risk: Implications for Management. ME Sherman, WD Foulkes, JNCI: Journal of the National Cancer Institute, Volume 113, Issue 9, September 2021, Pages 1127–1128, https://doi.org/10.1093/jnci/djab037 https://academic.oup.com/jnci/article/113/9/1127/6169004 In this issue of the Journal, de Jonge et al. (1) provide the strongest evidence to date that *BRCA1* and *BRCA2* germline pathogenic variants (GPVs) are associated with increased endometrial cancer (EC) risk. Among 5980 women with GPVs within the Hereditary Breast and Ovarian cancer study, the Netherlands (HEBON), they report that GPVs confer increased EC risk versus the general Dutch population (*BRCA1*, standardized incidence ratio = 3.51, 95% confidence interval = 2.61 to 4.72; *BRCA2*, standarized incidence ratio = 1.70, 95% confidence interval = 1.01 to 2.87) and that *BRCA1* GPV heterozygotes experience higher EC risk compared with HEBON participants whose relatives bear GPVs but who themselves tested negative. EC risks were higher among *BRCA1* GPV heterozygotes and for aggressive subtypes, such as those with serous histology or *TP53* somatic mutations. Most previous studies addressing EC risk among *BRCA1* and *BRCA2* GPV heterozygotes have been limited by small sample sizes and/or shorter follow-up (as reviewed in this publication). Although several prior reports have failed to show a statistically significant increased EC risk among heterozygotes, the power of such analyses to detect such risks has often been limited. Notably, 1 large observational study found that both *BRCA1* and *BRCA2* GPVs were associated with increased EC risk (odds ratio of 3.09 and 2.35, respectively) (2), and 2 smaller studies, focused on the serous subtype (3,4), found substantially increased (but almost certainly inflated) risks for this subtype. One recent systematic review and meta-analysis concluded that women bearing GPVs are at statistically significantly higher risk of developing EC, and especially serous EC, which they contend may be part of the "*BRCA1/2* syndrome" (5), whereas another systematic analysis found only modestly increased risks (6). Both reports suggest that the decision to undergo hysterectomy at risk-reducing surgery should reflect personal considerations.

Strengths of the current study include the large sample size, lengthy follow-up, pathology review, and quality of the data and analysis. Nonetheless, futures studies are needed to define absolute risks among the youngest women with *BRCA1* and *BRCA2* GPVs and in racially and ethnically diverse populations.

Dramatic increases in incidence and mortality rates related to EC consequent to the obesity epidemic have garnered attention (7), but opportunities for early detection and prevention of EC in genetically disposed high-risk groups have received less emphasis. Genetic risks for EC pose unique considerations, especially for cancer screening and prevention.

GPV heterozygotes face choices about whether to undergo risk-reducing surgery, the timing of such surgery, and the extent of surgery needed, which may include salpingectomy with deferred oophorectomy, bilateral salpingo-oophorectomy, and potentially, hysterectomy. If incidental cancers are found with risk-reducing surgery, additional quandaries about the need for staging and therapy arise.

Effective surveillance of GPV heterozygotes for EC would need to be long-term; of 19 serous-like ECs in HEBON among carriers, 6 were diagnosed between ages 40 and 60 years and 13 were diagnosed at later ages. Additionally, among women who retain their uteri, EC risk may affect decisions about breast cancer chemoprevention and adjuvant therapy for those affected, because tamoxifen increases EC risk, whereas aromatase inhibitors may lower EC risk (8). Finally, a woman's decision to retain her uterus limits her choice of menopausal hormone therapy to regimens containing both estrogen and

progesterone, which increases risk of breast cancer but not EC; estrogen-only options elevate EC risk and would be contraindicated (9). These considerations are critical as early oophorectomy increases risks of chronic diseases and mortality (10,11).

The pathogenesis of serous ECs is poorly understood. Serous ECs are diagnosed 5-10 years later, on average, than endometrioid ECs, and incident rates are higher among African American women, for unknown reasons. It has been hypothesized that serous cancers may develop from the surface endometrial epithelium, rather than from endometrial hyperplasia, the best recognized precursor of the endometrioid subtype (12). In fact, serous endometrial intraepithelial carcinoma (EIC), the presumptive precursor of uterine serous cancers, resembles serous tubal intraepithelial carcinoma (STIC) morphologically; both lesions demonstrate replacement of benign epithelium with high-grade malignant cells that bear *TP53* mutations. Discrete tubal lesions resembling STIC are found concurrently with serous ECs in about 10%-20% of cases (13), and EIC, like STIC, may present with metastatic disease, even without invasion in the uterus or fallopian tube, respectively.

Failure to identify STIC in many cases of high-grade serous tubo-ovarian cancer has prompted speculations that exfoliation of mutated cells from the fimbria of the tube into the peritoneum could account for such cases (14); however, the possibility that "normal appearing" endometrial cells bearing *TP53* mutations or tiny unrecognized EIC lesions could represent another source has not been fully explored. Given the suggestion that serous EC may not respond to standard tubo-ovarian chemotherapy, increased efforts to accurately assign primary sites of serous cancers may have future value in defining treatments (15).

Although de Jonge et al. (1) cautiously conclude that it is inappropriate to routinely recommend hysterectomy at the time of risk-reducing surgery, we consider that this is a suitable subject for review by professional bodies such as the Society of Gynecological Oncology, which should include the viewpoints of women facing these decisions. Importantly, whereas all diagnoses of tubo-ovarian carcinomas prompt discussions with patients about genetic testing, the need for testing after a diagnosis of uterine serous carcinomas is not addressed by guidelines, even when the diagnosis occurs at an uncharacteristically young age. Given the potential that high-grade serous carcinomas arising in the fallopian tube, ovary, endometrium, and peritoneum may all share associations with GPVs and that primary sites are not always discernible, we think that all women receiving these diagnoses should be offered genetic testing for *BRCA1*, *BRCA2*, and other *BRCA*-related genes implicated in homologous recombination repair, at time of diagnosis.

In summary, although the excellent study by de Jonge and colleagues provides solid evidence that *BRCA1* and *BRCA2* GPVs increase EC risk by at least two- to threefold, additional large, high-quality studies in diverse populations are needed, especially among African Americans for whom serous EC rates are notably elevated. Studies to define precise absolute age-specific EC risks for specific GPVs in *BRCA1* and in *BRCA2* and research on the biology of serous cancers are needed to derive evidence-based guidelines.

Endometrial Cancer Risk in Women With Germline *BRCA1* or *BRCA2* Mutations: Multicenter Cohort Study. MM de Jonge, CD de Kroon, DJ Jenner, J Oosting, JA de Hullu, MJE Mourits, EB Gómez Garcia, MGEM Ausems, JM Collée, K van Engelen, I van de Beek, The Hebon Group, VTHBM Smit, MA Rookus, GH de Bock, FE van Leeuwen, T Bosse, OM Dekkers, CJ van Asperen. *JNCI: Journal of the National Cancer Institute*, Volume 113, Issue 9, September 2021, Pages 1203–1211, https://doi.org/10.1093/jnci/djab036 https://academic.oup.com/jnci/article/113/9/1203/6169002

Background Endometrial cancer (EC) risk in BReast CAncer gene 1/2 (BRCA1/2) mutation carriers is uncertain; therefore, we assessed this in a large Dutch nationwide cohort study.

Methods We selected 5980 BRCA1/2 (3788 BRCA1, 2151 gBRCA2, 41 both BRCA1/BRCA2) and 8451 non-BRCA1/2 mutation carriers from the Hereditary Breast and Ovarian cancer study, the Netherlands cohort. Follow-up started at the date of the nationwide Dutch Pathology Registry coverage (January 1, 1989) or at the age of 25 years (whichever came last) and ended at date of EC diagnosis, last follow-up, or death (whichever came first). EC risk in BRCA1/2 mutation carriers was compared with 1) the general population, estimating standardized incidence ratios (SIRs) based on Dutch population-based incidence rates; and 2) non-BRCA1/2 mutation carriers, using Cox-regression analyses, expressed as hazard ratio (HR). Statistical tests were 2-sided.

Results Fifty-eight BRCA1/2 and 33 non-BRCA1/2 mutation carriers developed EC over 119 296 and 160 841 person-years, respectively (SIR = 2.83, 95% confidence interval [CI] = 2.18 to 3.65; and HR = 2.37, 95% CI = 1.53 to 3.69, respectively). gBRCA1 mutation carriers showed increased risks for EC overall (SIR = 3.51, 95% CI = 2.61 to 4.72; HR = 2.91, 95% CI = 1.83 to 4.66), serous-like EC (SIR = 12.64, 95% CI = 7.62 to 20.96; HR = 10.48, 95% CI = 2.95 to 37.20), endometrioid EC (SIR = 2.63, 95% CI = 1.80 to 3.83; HR = 2.01, 95% CI = 1.18 to 3.45), and TP53-mutated EC (HR = 15.71, 95% CI = 4.62 to 53.40). For BRCA2 mutation carriers, overall (SIR = 1.70, 95% CI = 1.01 to 2.87) and serous-like EC risks (SIR = 5.11, 95% CI = 1.92 to 13.63) were increased compared with the general population. Absolute risks by 75 years remained low (overall EC = 3.0%; serous-like EC = 1.1%).

Conclusions BRCA1/2 mutation carriers have a two- to threefold increased risk for EC, with highest risk observed for the rare subgroups of serous-like and p53-abnormal EC in BRCA1 mutation carriers.

Tables of contents for Gynecologic Oncology:
https://www.sciencedirect.com/journal/gynecologic-oncology/vol/162/issue/3

---

[*] ***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).