Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer.

BACKGROUND Classification of endometrial carcinomas (ECs) by morphologic features is irreproducible and imperfectly reflects tumor biology. The authors developed the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), a molecular classification system based on The Cancer Genome Atlas genomic subgroups, and sought to confirm both feasibility and prognostic ability in a new, large cohort of ECs.

METHODS Immunohistochemistry (IHC) for the presence or absence of mismatch repair (MMR) proteins (to identify MMR deficiency [MMR-D]), sequencing for polymerase-ε (POLE) exonuclease domain mutations (POLE EDMs), and IHC for tumor protein 53 (p53) (wild type vs null/missense mutations; p53 wt and p53 abn, respectively) were performed on 319 new EC samples. Subgroups were characterized and assessed relative to outcomes. The prognostic ability of ProMisE was compared with that of current risk-stratification systems (European Society of Medical Oncology [ESMO]).

RESULTS ProMisE decision-tree classification achieved categorization of all cases and identified 4 prognostic subgroups with distinct overall, disease-specific, and progression-free survival (P < .001). Tumors with POLE EDMs had the most favorable prognosis, and those with p53 abn the worst prognosis, and separation of the 2 middle survival curves (p53 wt and MMR-D) was observed. There were no significant differences in survival between the ESMO low-risk and intermediate-risk groups. ProMisE improved the ability to discriminate outcomes compared with ESMO risk stratification. There was substantial overlap (89%) between the p53 abn and high-risk ESMO subgroups; but, otherwise, there were no predictable associations between molecular and ESMO risk groups.

CONCLUSIONS Molecular classification of ECs can be achieved using clinically applicable methods and provides independent prognostic information beyond established clinicopathologic risk factors available at diagnosis. Consistent, biologically relevant categorization enables stratification for clinical trials and/or targeted therapy, identification of women who are at increased risk of having Lynch syndrome, and may guide clinical management.

Vulvar and vaginal melanoma: A unique subclass of mucosal melanoma based on a comprehensive molecular analysis of 51 cases compared with 2253 cases of nongynecologic melanoma.
JY Hou MD, C Baptiste, RB Hombalegowda, AI Tergas, R Feldman, NL Jones, S Chatterjee-Paer, A Bus-Kwofsk, JD Wright, WM Burke Cancer Early view DOI: 10.1002/cncr.30473

BACKGROUND Optimal treatments for vulvar and vaginal melanomas (VVMs) have not been identified. Herein, the authors compare molecular profiles between VVM and nongynecologic melanoma (NGM) subtypes with the objective of identifying novel, targetable biomarkers.

METHODS In total, 2304 samples of malignant melanoma that were submitted to Caris Life Sciences between 2009 and 2015 were reviewed. In situ hybridization and immunohistochemistry were used to assess copy numbers and protein expression of selected genes. Sequenced variants were analyzed using a proprietary cancer panel.

RESULTS In total, 51 VVMs (14 vaginal and 37 vulvar melanomas) were compared with 2253 malignant NGMs, including 2127 cutaneous, 105 mucosal, and 21 acral melanomas. In VVMs, B-Raf proto-oncogene serine/threonine kinase (BRAF) was the most frequently mutated gene (26%) compared with 8.3% of mucosal NGMs (P = .008). In BRAF-mutated tumors, fewer VVMs (50%), compared with NGMs (82.1%), had a variant within the valine codon 600 (V600) domain. The KIT mutation rate was highest in VVMs (22%) compared with 3% in cutaneous (P < .001) and 8.8% in mucosal (P = .05) melanoma subtypes. NRAS mutations were rare in VVMs compared with cutaneous (25.9%; P = .009) and acral (40.6%; P = .002) melanoma subtypes. PD-L1 (56%) and PD-1 (75%) were frequently expressed in VVM, whereas PI3KCA pathway mutations and estrogen receptor/progesterone receptor expression were rare. Compared with VVMs that had

**BACKGROUND** The incidence of endometrial cancer among young women is increasing. Some patients with low-grade endometrial cancer receive hormone therapy (HT) before surgery to preserve fertility. It is unclear whether this adversely affects survival.

**METHODS** Patients with localized, low-grade endometrial cancer who were aged <45 years were selected from the Surveillance, Epidemiology, and End Results database between 1993 and 2012. Propensity score matching was used to select comparable groups receiving HT or primary surgery. Cancer-specific and overall survival were measured using Kaplan-Meier methods. Hazard ratios and 95% confidence intervals (95% CIs) were estimated using Cox models adjusted for age, period of diagnosis, marital status, race, tumor grade, morphology, and previous radiotherapy.

**RESULTS** A total of 6339 women were included in the current study cohort, 161 of whom initially received HT and 6178 of whom received primary surgery. After 15 years of follow-up, all-cause mortality did not differ between the groups (HT group: 14.1% [95% CI, 6.7%-28.4%] and propensity score-matched primary surgery group: 9.3% [95% CI, 4.1%-20.5%]). Cancer-specific mortality appeared higher in patients treated with HT compared with those treated with primary surgery (9.2% [95% CI, 3.4%-24.0%] vs 2.1% [95% CI, 1.5%-2.8%]). However, this difference was driven by 3 late deaths in the HT group. Sensitivity analyses using a broader definition of cancer-specific mortality provided no statistical evidence of a survival difference between the treatment groups. The hazard ratio for the overall risk of death was 1.45 (95% CI, 0.44-4.74).

**CONCLUSIONS** Based on this population-based cohort, young patients with low-grade endometrial cancer appear to have excellent survival, regardless of the primary therapy chosen (HT vs primary surgery). The current selection of patients for HT to preserve fertility, which is managed carefully by experienced clinicians, does not appear to significantly worsen clinical outcomes.


**BACKGROUND** The purpose of this study was to determine the effect of retroperitoneal (RP) exploration on progression-free survival (PFS) and overall survival (OS) in epithelial ovarian cancer (EOC) patients with stage IIIC disease who underwent optimal debulking surgery.

**METHODS** Data were collected from records of the Gynecologic Oncology Group (GOG-182) study of stage IIIC EOC patients cytoreduced to no gross residual disease (R0) or minimal gross residual (<1 cm) disease (MGRD) at primary surgery. Patients with stage IIIC disease by intraperitoneal (IP) tumor were included and divided into three groups: 1) > 2 cm IP tumor without lymph node involvement (IP/RP-), 2) > 2 cm IP tumor with lymph node involvement (IP/RP+), and 3) > 2 cm IP tumor with no RP exploration (IP/RP?). The effects of disease distribution and RP exploration on PFS and OS were assessed using Kaplan-Meier and proportional hazards methods.

**RESULTS** There were 1871 stage IIIC patients in GOG-182 who underwent optimal primary debulking surgery. Of these, 689 (36.8%) underwent RP exploration with removal of lymph nodes from at least 1 para-aortic site, and 1182 (63.2%) did not. There were 269 patients in the IP/RP- group, 420 patients in the IP/RP+ group, and 1182 patients in the IP/RP? group. Improved PFS (18.5 vs 16.0 months; P < .0001) and OS (53.3 vs 42.8 months; P < .0001) were associated with RP exploration versus no exploration. Patients with MGRD had improved PFS (16.8 vs 15.1 months, P = 0.0108) and OS (44.9 vs 40.5 months, P = 0.0076) versus no exploration.

**CONCLUSIONS** RP exploration at the time of primary surgery in patients with optimally debulked stage IIIC EOC is associated with a survival benefit.


**BACKGROUND** Mesothelial vascular cell adhesion molecule-1 (VCAM-1) expression in the metastatic epithelial ovarian cancer (EOC) microenvironment is induced by tumor and mediates tumor cell invasion. VCAM-1 imaging suggests expression during treatment is an indicator of platinum resistance. Here, we assess the potential prognostic

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significance of mesothelium VCAM-1 expression and prospectively evaluate whether soluble VCAM-1 (sVCAM-1) is a surrogate for mesothelial expression.

**METHODS** A retrospective review of EOC patients was performed to evaluate outcomes with mesothelium VCAM-1 expression determined by immunohistochemistry of peritoneum or omentum specimens. A prospective cohort of EOC patients was identified and followed through primary treatment. Serum for sVCAM-1 evaluation, which was performed via enzyme-linked immunosorbent assay, was collected before surgery or neoadjuvant chemotherapy and at each treatment cycle. Peritoneal specimens were obtained during debulking to assess mesothelial VCAM-1 expression.

**RESULTS** A retrospective review identified 54 advanced-stage EOC patients. Patients expressing mesothelium VCAM-1 had shortened overall survival (44 vs 79 months, P = 0.035) and progression-free survival (18 vs 67 months, P = 0.010); the median time to platinum resistance was 36 months for VCAM-1-expressing patients and not yet determined for the VCAM-1-negative group. In our prospective observational cohort, 18 EOC patients completed primary treatment; 3 were negative for mesothelium VCAM-1 expression, and sVCAM-1 did not vary between groups.

**CONCLUSIONS** Mesothelium VCAM-1 expression is negatively associated with progression-free and overall survival in EOC. This is especially compelling in light of previous data suggesting that persistent VCAM-1 expression during treatment is an indicator of platinum resistance. Our pilot study had insufficient cases to determine whether sVCAM-1 would substitute for mesothelium expression.

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A paradox of DNA biology is that sequence integrity must be maintained in order for the organism to maintain life and normal functions, yet evolution requires some variability in gene expression so that changes that are more adaptive are positively selected. Indeed, more highly evolved species have developed an immune system that protects organisms against the world of dangers as a direct consequence of focusing DNA mutation on a particular subset of genes that encode for antigen receptors. However, in general, environmental and biologic insults that disrupt the DNA sequence (and there are many of these, including ultraviolet light, mutagens in cigarettes and some foods, and even free radicals generated by normal metabolic processes) have the potential to be deleterious, and a complex array of DNA-repair mechanisms have developed to maintain sequence integrity within fairly well-circumscribed limits. One classification of DNA-damaging effects includes those that cause single-stranded DNA breaks and those that cause double-stranded DNA breaks. Double-stranded breaks are more likely to be fatal to the cell. Single-stranded breaks are normally repaired by at least three mechanisms: nucleotide excision repair, base excision repair (the most commonly used of the three), and mismatch repair. Genetic defects in these mechanisms are associated with disease states, which indicates their importance. As examples, xeroderma pigmentosum is associated with defects in nucleotide excision repair, familial adenomatous polyposis is associated with defects in base excision repair, and the Lynch syndrome is associated with mismatch repair defects. At least two complex mechanisms are involved in the repair of double-stranded DNA breaks: homologous recombination and nonhomologous end joining. As the names imply, homologous recombination fixes the break and restores the original sequence; nonhomologous end joining is error-prone. Genetic diseases that affect these repair mechanisms include BRCA1 and BRCA2 mutations, which interfere with homologous recombination, and the Nijmegen breakage syndrome (associated with microcephaly, short stature, and characteristic facies, along with immunodeficiency, radiation sensitivity, and a predisposition to lymphoid cancer), which affects nonhomologous end joining. One approach to cancer treatment is to kill a cancer cell by inducing double-stranded DNA breaks through chemotherapy or radiation. The cancer cell combats this approach by using its DNA-repair mechanisms to repair the damage induced by radiation and DNA-targeting drugs. Thus, one possible mechanism to enhance the antitumor effects of such cancer treatments might be to inhibit the DNA-repair mechanisms. The development of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors is based on this rationale. PARP inhibitors interfere with DNA repair in several ways. They prevent base excision repair, which leaves single-stranded breaks un repaired and increases the susceptibility of the cell to a second DNA-damaging hit.1 They may also act to retard homologous recombination by failing to detect stalled replication sites2 and enhance the error-prone nonhomologous end joining by binding to DNA kinase. The clinical development of PARP inhibitors has been a major emphasis in ovarian cancer therapy during the past several years. The initial approval of olaparib for this indication 2 years ago in the United States opened the door to the first routine use of this agent. In this issue of the Journal, Mirza et al.4 describe the success of another PARP inhibitor, niraparib, in significantly extending the duration of progression-free survival among women with platinum-sensitive, recurrent ovarian cancer. Other PARP inhibitors are in development. The target affinity for various PARP species, off-target effects, and pharmacokinetics vary among the newer PARP inhibitors; they may not be interchangeable, and resistance to one may not mean resistance to all (cross-resistance). Maximizing the utility of these new agents will require answers to important clinical questions. Which patients with ovarian cancer will benefit from PARP inhibitors? In early studies, the benefits of olaparib appeared to be limited to the 10% of patients with germline mutations in BRCA1 and BRCA2. The study by Mirza et al. appears to also show significant activity in patients with somatic BRCA mutations and even in patients without evidence of BRCA1/2 mutations. These findings have the potential to greatly expand the population of patients who can benefit from this new class of therapeutic agents. Additional testing in patients with triple-negative breast cancer (ClinicalTrials.gov number, NCT00813956), pancreatic cancer (NCT00515866), and other cancers
(NCT02286687) may expand the populations further. When will the PARP inhibitors be most beneficial during ovarian treatment? The findings of Mirza et al. confirm the work of Ledermann et al.5 and establish the major utility of PARP inhibition as maintenance therapy after platinum treatment for recurrent disease. Platinum–PARP inhibitor combinations as initial therapy (e.g., NCT00989651) and single-agent maintenance during first remission (e.g., NCT02470585) are also in clinical trial. In the United States, the PARP inhibitor olaparib is currently approved for the treatment of measurable cancer after several other therapies. It will be challenging to define the most effective treatment regimen for first-line therapy as the goal changes from extended survival to enhanced cure rates. Classic chemotherapy questions remain to be answered as well. How long should the PARP inhibitor be continued, particularly as maintenance therapy in patients with no measurable disease? What are the best chemotherapy agent partners? Combinations of carboplatin and a PARP inhibitor may increase the stress on the DNA-repair pathways. Alternatively, could a PARP inhibitor like niraparib substitute for carboplatin in some therapeutic settings? Will PARP inhibitors and platinum complexes prove to be cross-resistant? The answers to all these questions are not clear, but it is apparent that this new class of agents has the potential to change the therapy of ovarian cancer in ways that have not been seen since the introduction of paclitaxel in 1993. The curative potential of these drugs has not been established, but treatment with PARP inhibitors will certainly help women with ovarian cancer to live longer and better. It is now up to the oncology community to maximize those benefits in ovarian cancer and extend them to other patients with BRCA-related cancers.


The clinical utility of genomic cancer risk assessment for cancer predisposition is well established.1 Clinicians who provide these services are dependent on clinical laboratory reports of genetic test results to inform their recommendations for patients about cancer screening, risk management, and targeted genomic therapies. For nearly two decades, genomic cancer risk assessment was restricted to high-penetrance genes with proven clinical utility, such as BRCA1, BRCA2, APC, and the Lynch syndrome associated genes (MLH1, MSH2, MSH6, and PMS2).2 And testing was only available through a small number of Clinical Laboratory Improvement Amendments-approved laboratories. However, the advent of lower-cost next-generation sequencing and the Supreme Court’s decision to invalidate the patent on testing for BRCA1 and BRCA23 has moved the field beyond phenotype-specific single-gene testing to large-scale multigene panel testing that is heavily marketed to clinicians by a growing number of commercial laboratories. The bundling of low and moderate penetrance genes with questionable or unknown clinical utility into multigene panels has complicated the translation of genetic test results into risk-appropriate clinical care.4 Adding significantly to this complexity are inconsistencies in the interpretation and classification of genetic variants by different laboratories. Factors that contribute to these inconsistencies include inexperienced laboratories, lack of rules to harmonize approaches to the classification and curation of variants, and discrepancies among curators about how to weight multifactorial models for variant classification across diverse genes. Before multigene panel testing, only a few variant databases existed, such as Breast Cancer Information Core (https://research.nih.gov/bic/) for BRCA1 and BRCA2 variants. Although initially useful and representative of variants in the United States, the utility of the Breast Cancer Information Core database ultimately diminished due to cessation of commercial laboratory contributions, inadequate curation, and uncertainty about quality of evidence needed for a given variant classification. Other long-established databases include the International Society for Gastrointestinal Hereditary Tumors (http://insight-group.org/) and the International Agency for Research on Cancer (https://www.iarc.fr/). However, all these efforts need to evolve to address the breadth of genes on multigene panels, especially because there is a paucity of validated functional assays to incorporate into active variant classification programs. Emerging variant databases such as ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), Leiden Open Variation Database (www.lovd.nl), and related working groups are striving to harmonize variant classifications across the spectrum of clinically used genes. ClinVar allows commercial laboratory entities to upload and share variants with classifications. It incorporates a four-star system regarding the strength of classification data submitted on a particular variant, from single-case variant submissions with no or limited interpretation (1 to 2 stars), to stronger evidence-based submissions reviewed by an expert panel, such as the Evidenced-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) or International Society for Gastrointestinal Hereditary Tumors (three stars), to established variants that have been incorporated into practice guidelines (four stars; only 23 entries to date5). ENIGMA is an international academic consortium of investigators with active working groups considering functional assays, splicing, pathology, and clinical applications. ClinVar encourages use of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology variant-classification guidelines.7 The guidelines provide rules to aid in the interpretation of DNA-based variants, ranking variants in the following order of pathogenicity: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign.7 In a recent publication wherein the use of the ACMGG guidelines was assessed on 1,640 variants from whole-exome sequencing of 404 individuals, it was noted that expert interpretive judgment was essential to classify variants using ACMGG guidelines.8 The concordance is highest for actionable dominant cancer genes (95%), and less so for recessive cancer and noncancer genes. In the article that accompanies this editorial, Balmaña et al.9 describe conflicting interpretations of variants reported by commercial laboratories in non-BRCA cancer predisposition genes that were submitted to the Prospective Registry Of

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Clinical laboratories, as reported to the Prospective Registry of Multiplex Testing (PROMPT), an online genetic registry, describe conflicting variant interpretations between Clinical Laboratory Improvement Amendments–approved commercial laboratories and providers may differ and lead to conflicting reporting and, potentially, to inappropriate medical management. We suspect susceptibility. Guidelines are available for variant classification; however, interpretation of these guidelines by laboratories may limit representative enrollment and clinical data quality and/or documentation. It is estimated that less than 5% of variants reported through multigene panel testing are currently represented in the PROMPT database, and nearly 30% of enrolled patients \( (n = 299) \) had to be excluded from this study because of incomplete information provided by the research participants. Beyond limited accrual due to volunteer bias, self-enrollment is Web-based, so concerns about identity theft or disclosure of protected health information may reduce patient participation. The majority of participants reported that they were invited to PROMPT by their health-care provider and/or the clinical genetic-testing laboratory, reinforcing the value of engaging professionals in recruitment efforts. Another limitation is the focus on patients in the United States, which limits global accrual. Data from PROMPT will be most powerful when combined with data from complementary approaches such as ENIGMA or the Clinical Cancer Genomics Community Research Network, clinician-driven international research initiatives, and other academic consortia and commercial partnerships. The Balmaña et al study provides a glimpse of the variant classification iceberg, and the challenges cited here urgently need to be addressed because they are likely to be magnified by the inevitable transition to using whole-exome/genome testing in clinical care to determine cancer risks and etiology. Further, rapidly expanding use of tumor/germline sequencing in precision medicine adds another dimension to the same variant classification problems. The Food and Drug Administration is considering a new rule that would accept annotation in a database like ClinVar as adequate clinical validity for laboratories performing molecular diagnostic tests (eg, companion diagnostics). Therefore, transparency and consistency in variant classification and nomenclature are critical, in addition to adequate resources to support harmonization efforts. The fruits of improved variant classification should also be applied to patients whose VUS is reclassified—a daunting task with mobile populations and changing health-care delivery models. Well-designed patient- and clinician-driven research initiatives are powerful tools to promote accurate variant curation and elucidation of the genetic epidemiology of cancer. Finally, clinician engagement in continuing evidence-based education and patient-centered support is crucial to enable scrutiny of genetic variants and adoption of evolving practice policies and risk-appropriate management guidelines, all to promote best practices in the integration of rapidly evolving genomic tools into practice.

### Conflicting Interpretation of Genetic Variants and Cancer Risk by Commercial Laboratories as Assessed by the Prospective Registry of Multiplex Testing


**Purpose** Massively parallel sequencing allows simultaneous testing of multiple genes associated with cancer susceptibility. Guidelines are available for variant classification; however, interpretation of these guidelines by laboratories and providers may differ and lead to conflicting reporting and, potentially, to inappropriate medical management. We describe conflicting variant interpretations between Clinical Laboratory Improvement Amendments–approved commercial clinical laboratories, as reported to the Prospective Registry of Multiplex Testing (PROMPT), an online genetic registry.
Methods Clinical data and genetic testing results were gathered from 1,191 individuals tested for inherited cancer susceptibility and self-enrolled in PROMPT between September 2014 and October 2015. Overall, 518 participants (603 genetic variants) had a result interpreted by more than one laboratory, including at least one submitted to ClinVar, and these were used as the final cohort for the current analysis.

Results Of the 603 variants, 221 (37%) were classified as a variant of uncertain significance (VUS), 191 (32%) as pathogenic, and 34 (6%) as benign. The interpretation differed among reporting laboratories for 155 (26%). Conflicting interpretations were most frequently reported for CHEK2 and ATM, followed by RAD51C, PALB2, BARD1, NBN, and BRIP1. Among all participants, 56 of 518 (11%) had a variant with conflicting interpretations ranging from pathogenic/likely pathogenic to VUS, a discrepancy that may alter medical management.

Conclusions Conflicting interpretation of genetic findings from multiplex panel testing used in clinical practice is frequent and may have implications for medical management decisions.


Background Borderline ovarian tumors are generally diagnosed in young women. Because of the young age of patients at first diagnosis and at recurrence, and given the good prognosis of borderline ovarian tumors, a conservative surgical approach in those women who wish to preserve their fertility is advised. In this scenario, transvaginal ultrasound examination plays a key role in the detection of borderline ovarian tumor recurrence, and in assessment of amount of normal functioning parenchyma remaining. To date, no data are available about the natural history of borderline ovarian tumor recurrence.

Objective The aim of the study was to determine growth rate of recurrent ovarian cysts by a scheduled follow-up by ultrasound examination, in women previously treated with fertility-sparing surgery due to borderline ovarian tumors.

Study Design In this prospective observational study, we collected data from 34 patients previously treated with fertility-sparing surgery due to borderline ovarian tumors, who had a suspicious recurrent lesion. The patients underwent transvaginal ultrasonographic examination every 3 months, until the clinical setting recommended proceeding with surgery. According to cyst size at study entry, they were categorized into 3 groups: ≤10 mm, 10-20 mm, and >20 mm. Summary statistics for cyst size, growth rate, and the probability of remaining within the same dimension category at first ultrasound during the follow-up were also obtained. For each cyst the growth rate was calculated as the slope of the linear interpolation between 2 consecutive measurements.

Results Follow-up timing ( P < .001), cyst size ( P < .001), and micropapillary pattern ( P < .001) were factors significantly affecting the cyst growth both in univariate and multivariate analysis. According to size category at first ultrasound, growth rate ranges from a minimum of 0.06 mm/mo for cysts <10 mm up to 1.92 mm/mo for cysts >20 mm. The final histology of all recurrent lesions confirmed the same histotype of primary borderline ovarian tumors.

Conclusion This article represents the first observational study that describes the trend in the growth rate of borderline ovarian tumor recurrence in relation to their size detected at the first ultrasound examination. The findings of this study seem to confirm, in selected patients, that a thorough ultrasonographic follow-up of borderline ovarian tumor recurrence has proven to be safe and feasible. The final goal of such management is to maximize the impact on fertility potential of these young women without worsening their prognosis.


Abstract Cancer cells actively promote their tumorigenic behavior by reprogramming gene expression. Loading intraluminal vesicles with specific miRNAs and releasing them into the tumor microenvironment as exosomes is one mechanism of reprogramming whose regulation remains to be elucidated. Here, we report that miR-6126 is ubiquitously released in high abundance from both chemosensitive and chemoresistant ovarian cancer cells via exosomes. Overexpression of miR-6126 was confirmed in healthy ovarian tissue compared with ovarian cancer patient samples and correlated with better overall survival in patients with high-grade serous ovarian cancer. miR-6126 acted as a tumor suppressor by directly targeting integrin-β1, a key regulator of cancer cell metastasis. miR-6126 mimic treatment of cancer cells resulted in increased miR-6126 and decreased integrin-β1 mRNA levels in the exosome. Functional analysis showed that treatment of endothelial cells with miR-6126 mimic significantly reduced tube formation as well as invasion and migration capacities of ovarian cancer cells in vitro. Administration of miR-6126 mimic in an orthotopic mouse model of ovarian cancer elicited a relative reduction in tumor growth, proliferating cells, and microvessel density. miR-6126 inhibition promoted oncogenic behavior by leading ovarian cancer cells to release more exosomes. Our findings provide new insights into the role of exosomal miRNA-mediated tumor progression and suggest a new therapeutic approach to disrupt oncogenic phenotypes in tumors.

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Chromosome instability drives phenotypic switching to metastasis. CF Gaoa, Y Sua, J Koemanb, E Haaka, K Dykemab, C Essenberga, E Hudsonb, D Petilloc, SK Khood, GF Vande Wouded. PNAS vol. 113 no. 51 > ChongFeng Gao, 14793–14798, doi: 10.1073/pnas.1618215113
http://www.pnas.org.ezproxy.uky.edu/content/113/51/14793.full
Abstract  Chromosome instability (CIN) is the most striking feature of human cancers. However, how CIN drives tumor progression to metastasis remains elusive. Here we studied the role of chromosome content changes in generating the phenotypic dynamics that are required for metastasis. We isolated epithelial and mesenchymal clones from human carcinoma cell lines and showed that the epithelial clones were able to generate mesenchymal variants, which had the potential to further produce epithelial revertants autonomously. The successive acquisition of invasive mesenchymal and then epithelial phenotypes recapitulated the steps in tumor progression to metastasis. Importantly, the generation of mesenchymal variants from clonal epithelial populations was associated with subtle changes in chromosome content, which altered the chromosome transcriptome and influenced the expression of genes encoding intercellular junction (IJ) proteins, whereas the loss of chromosome 10p, which harbors the ZEB1 gene, was frequently detected in epithelial variants generated from mesenchymal clones. Knocking down these IJ genes in epithelial cells induced a mesenchymal phenotype, whereas knocking down the ZEB1 gene in mesenchymal cells induced an epithelial phenotype, demonstrating a causal role of chromosome content changes in phenotypic determination. Thus, our studies suggest a paradigm of tumor metastasis: primary epithelial carcinoma cells that lose chromosomes harboring IJ genes acquire an invasive mesenchymal phenotype, and subsequent chromosome content changes such as loss of 10p in disseminated mesenchymal cells generate epithelial variants, which can be selected for to generate epithelial tumors during metastatic colonization.
Significance  Chromosome instability and its resulting karyotypic heterogeneity make up one of the most striking characteristics of human cancers. Yet whether chromosome loss or gain drives tumor progression to metastasis remains unknown. Here we show that clonal populations of epithelial cells spontaneously generate mesenchymal variants. These variants have potential for reverting to an epithelial phenotype. Importantly, we show that the successive phenotypic variants selectively eliminate or acquire chromosome segments that harbor genes encoding intercellular junctional proteins and their regulators. Thus, tumor metastasis can be a clonal process driven by chromosome instability.

Health-care providers are increasingly using targeted therapies and personalised medicine to treat patients with cancer. In ovarian cancer, tumours with BRCA gene mutations are being targeted by these treatments. BRCA1 and BRCA2 mutations are associated with 10–15% of all ovarian cancers, but with the addition of somatic mutations, about 50% of high-grade serous tumours (the commonest ovarian cancer subtype) will have some form of mutation. 1 Repairing DNA defects is a common natural event and if not achievable, cellular death occurs. There are two relevant pathways for repairing DNA defects: one acts on breaks in double-stranded DNA and requires a functioning BRCA gene, and a second repairs single-stranded DNA breaks. The second pathway is controlled by PARP enzymes whose action is blocked by olaparib. This blocking by olaparib then induces double-stranded DNA breaks, which in BRCA -mutated cells are irreparable, resulting in what is termed synthetic cell death. In The Lancet Oncology Ledermann and colleagues 3 present the overall survival with the use of olaparib in women with platinum-sensitive recurrent serous ovarian cancer. Notably, advanced ovarian cancer accounts for 75% of women at presentation and although tumours are very sensitive to platinum-based chemotherapy, disease relapse is common, as reflected in the 5-year survival rates of 40%. The phase 2 study 3 recruited 265 women who had at least two previous platinum-based treatments. Randomisation was 1:1 to olaparib 400 mg twice a day or placebo maintenance treatment, continued to tumour recurrence. 136 (51%) of 265 women in the trial had BRCA mutations. These mutations were germline in 116 tumours, and somatic in 20 tumours. The primary endpoint of the trial, progression-free survival, was previously reported 5 in 2012, showing a significant improvement with the addition of olaparib. In 2014, the team published a pre-planned analysis 6 of the outcome in participants with BRCA mutations. Overall survival was a secondary outcome for the study, and in the report by Ledermann and colleagues 3 the median follow-up time was 71-0 months (IQR 67-8–72-9) for the overall study population. The results suggested an improved overall survival for olaparib use in the whole population (HR 0·73 [95% CI 0·55–0·96]), but did not achieve the planned level for statistical significance. Median overall survival was 29-6 months (95% CI 26-9–35-7) in the olaparib group and 27-8 (24-9–33-7) in the placebo group. However, the results did show a significant improvement in overall survival in women with BRCA mutations (70% overall survival data maturity), with median overall survival of 34-9 months (29-2–54-6) in the olaparib group compared with 30-2 (23-1–40-7) in the placebo group (HR 0·62 [95% CI 0·41–0·94]; nominal p=0·025). This is therefore the first study showing an improved overall survival with olaparib in ovarian cancer treatment. However, a note of caution is required. If a study has not been powered to ascertain the differences in overall survival, this is akin to doing a non-pre-planned subgroup analysis, which is fraught with dangers. Therefore it is important to remember these limitations when interpreting the findings of this study. Nevertheless, irrespective of the multiple analytical approaches used, the consistent finding was an improved overall survival associated with olaparib in participants with BRCA mutations. This finding also aligns to the previously published

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improved progression-free survival. Some patients in this study were on olaparib treatment for years, suffering the drug’s known side-effects, but unfortunately the study does not detail how these side-effects affected their quality of life, which would have been useful. Olaparib use in ovarian cancer has mainly been reported in phase 2 studies in women with platinum-sensitive recurrent high grade serous disease comparing the drug with conventional treatment, maintenance treatment, or combined with other target treatments. In all of these studies, progression-free survival was the primary outcome and overall survival was not included. This approach to trials, using a surrogate marker for overall survival, in this case progression-free survival, is driven by the understandable desire to speed patient access to effective novel treatments. Awaiting the results of an overall survival analysis can delay this access by some years. Additionally, use of progression-free survival rather than overall survival to test the efficacy of treatments avoids the confounding issues associated with patients who have subsequent treatments that could affect the outcome. However, the assumption is that progression-free survival correlates with overall survival, which is not always the case. It would seem that research is needed to identify robust surrogate markers (that can be measured even earlier than progression-free survival) for overall survival, which, if identified, could change the face of clinical trials. Agreement with the relevant regulatory authorities would also be important. This study, which reports an overall survival advantage with olaparib and identifies patients who gain most benefit from the treatment, after accepting its caveats, is a welcome addition to treatment strategies. To apply the findings from this study into clinical practice would require that health-care providers screen women with high-grade serous ovarian cancers for BRCA mutations, which is not universally done at present. The provision of additional screening might need to be addressed as BRCA gene-targeted therapies gain momentum.


**Background** In patients with platinum-sensitive recurrent serous ovarian cancer, maintenance monotherapy with the PARP inhibitor olaparib significantly improves progression-free survival versus placebo. We assessed the effect of maintenance olaparib on overall survival in patients with platinum-sensitive recurrent serous ovarian cancer, including those with BRCA1 and BRCA2 mutations (BRCA m).

**Methods** In this randomised, placebo-controlled, double-blind, phase 2 trial involving 82 sites across 16 countries, patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more courses of platinum-based chemotherapy and had responded to their latest regimen were randomly assigned (1:1) using a computer-generated sequence to receive oral maintenance olaparib (as capsules; 400 mg twice a day) or a matching placebo by an interactive voice response system. Patients were stratified by ancestry, time to progression on penultimate platinum, and response to most recent platinum. Patients and investigators were masked to treatment assignment by the use of unique identifiers generated during randomisation. The primary endpoint of the trial was progression-free survival. In this updated analysis, we present data for overall survival, a secondary endpoint, from the third data analysis after more than 5 years’ follow-up (intention-to-treat population). We did the updated overall survival analysis, described in this Article at 77% data maturity, using a two-sided α of 0.05%. As the study was not powered to assess overall survival, this analysis should be regarded as descriptive and the p values are nominal. We analysed randomly assigned patients for overall survival and all patients who received at least one dose of treatment for safety. This trial is ongoing and is registered with ClinicalTrials.gov, number NCT00753545.

**Findings** Between Aug 28, 2008, and Feb 9, 2010, 265 patients were randomly assigned to olaparib (n=136) or placebo (n=129). 136 patients had deleterious BRCA m. The data cutoff for this analysis was Sept 30, 2015. An overall survival advantage was seen with maintenance olaparib versus placebo in all patients (hazard ratio [HR] 0.73 [95% CI 0.55–0.96]; nominal p=0.025, which did not meet the required threshold for statistical significance [p<0.0095]; median overall survival was 29.8 months [95% CI 26.9–35.7] for those treated with olaparib vs 27.8 months [24.9–33.7] for those treated with placebo), and in patients with BRCA m (HR 0.62 [95% CI 0.41–0.94] nominal p=0.025; 34.9 months [95% CI 29.2–54.6] vs 30.2 months [23.1–40.7]). The overall survival data in patients with BRCA wild-type were HR 0.83 [95% CI 0.55–1.24], nominal p=0.37; 24.5 months [19.8–35.0] for those treated with olaparib vs 26.6 months [23.1–32.5] for those treated with placebo). 11 (15%) of 74 patients with BRCA m received maintenance olaparib for 5 years or more. Overall, common grade 3 or worse adverse events in the olaparib and placebo groups were fatigue (11 [8%] of 136 patients vs four [3%] of 128) and anaemia (eight [6%] vs one [1%]). 30 (22%) of 136 patients in the olaparib group and 11 (9%) of 128 patients in the placebo group reported serious adverse events. In patients treated for 2 years or more, adverse events in the olaparib and placebo groups included low-grade nausea (24 [75%] of 32 patients vs two [40%] of five), fatigue (18 [56%] of 32 vs two [40%] of five), vomiting (12 [38%] of 32 vs zero), and anaemia (eight [25%] of 32 vs one [20%] of five); generally, events were initially reported during the first 2 years of treatment.

**Interpretation** Despite not reaching statistical significance, patients with BRCA-mutated platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy after platinum-based chemotherapy appeared to have longer overall survival, supporting the reported progression-free survival benefit. Clinically useful long-term exposure
to olaparib was seen with no new safety signals. Taken together, these data support both the long-term clinical benefit and tolerability of maintenance olaparib in patients with BRCA-mutated platinum-sensitive recurrent serous ovarian cancer.

**Generic oncology drugs: are they all safe?**

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http://jamanetwork.com.ezproxy.uky.edu/journals/jamaoncology/fullarticle/2536198

Although the availability of generic oncology drugs allows access to contemporary care and reduces costs, there is international variability in the safety of this class of drugs. In this Series paper, we review clinical, policy, safety, and regulatory considerations for generic oncology drugs focusing on the USA, Canada, the European Union (EU), Japan, China, and India. Safety information about generic formulations is reviewed from one agent in each class, for heavy metal drugs (cisplatin), targeted agents (imatinib), and cytotoxic agents (docetaxel). We also review regulatory reports from Japan and the USA, countries with the largest pharmaceutical expenditures. Empirical studies did not identify safety concerns in the USA, Canada, the EU, and Japan, where regulations and enforcement are strong. Although manufacturing problems for generic pharmaceuticals exist in India, where 40% of all generic pharmaceuticals used in the USA are manufactured, increased inspections and communication by the US Food and Drug Administration are occurring, facilitating oversight and enforcement. No safety outbreaks among generic oncology drugs were reported in developed countries. For developing countries, oversight is less intensive, and concerns around drug safety still exist. Regulatory agencies should collaboratively develop procedures to monitor the production, shipment, storage, and post-marketing safety of generic oncology drugs. Regulatory agencies for each country should also aim towards identical definitions of bioequivalence, the cornerstone of regulatory approval.

**Routine Cancer Antigen 125 Surveillance—The Fatal Attraction of Testing.**


http://jamanetwork.com.ezproxy.uky.edu/journals/jamaoncology/fullarticle/2536198

The article by Esselen et al1 in this issue of JAMA Oncology belongs to the category of health services research that asks how the introduction of new evidence influences clinical practice. In the instance they examined—publication of a study that showed routine cancer antigen 125 (CA-125) surveillance was harmful—the answer seems to be "not at all." In the 6 NCI-designated cancer centers they studied, the use and frequency of CA-125 testing of women in remission after initial treatment for ovarian cancer was similar in the years before and after the study. In both periods, almost all such patients received CA-125 testing approximately every 3 to 4 months. This is actually quite a remarkable observation. Why did practice not change? It is instructive to reread the original study by Rustin et al2,3 that questioned the use of CA-125 testing. It was a well-conducted multicenter randomized trial of 529 women who were in remission after initial chemotherapy for ovarian cancer. All patients received CA-125 testing every 3 months, but the treating physicians did not know the results. If and when a CA-125 test exceeded twice normal, patients were randomized into what they called early and delayed treatment groups, with randomization stratified by several prognostic factors. For patients in the early treatment group, their physicians were notified of the CA-125 results. In the delayed treatment group the results were withheld, and any decisions about further treatment were based on clinical recurrence. Most women in the early treatment group started chemotherapy soon after the notification of elevated CA-125 results. Those in the delayed treatment group started about 5 months later. Median survival was not different: 25.7 months in the early treatment group vs 27.1 months in the delayed treatment group. However, median time to deterioration in global health score or death was significantly longer in the delayed treatment group (5.8 vs 3.2 months, P = .002). The delayed treatment group also underwent fewer cycles of chemotherapy, were less likely to receive third-line chemotherapy, and had 5 more months to live in remission after their initial treatment. The question for discussion then becomes: why was there no change in practice in response to good evidence? It is not as if physicians are incapable of rapid change in practice in the face of new information. It happens all the time when the information favors new or more treatment. For example, we assessed change in practice associated with the report showing a 2% absolute survival improvement at 18 months with taxane plus doxorubicin compared with doxorubicin alone in breast cancer patients with positive nodes. The oral report6 of these results in 1998, 5 years before the actual publication of the trial, was associated with a rapid shift to taxanes with a more than doubling in use within 3 months. Why did this not occur with the Rustin study? One could argue that there was no change because the clinical guidelines did not change. This is somewhat circular, because the 6 centers studied by Esselen et al1 were leading academic medical centers, populated by clinicians who also sit on the committees that write the guidelines. I will propose 2 sets of factors contributing to the lack of an obvious change in practice in response to the Rustin study. The first relates to the fundamental attractiveness of testing, and the second involves how the Rustin study was framed by the authors and subsequent commentators. Physicians practice in a sea of uncertainty. Making life-altering decisions based on incomplete information is 1 of the major stresses of becoming a physician. There are good and bad ways of dealing with that stress. Over confidence is 1 bad way. We all have encountered physicians who practice a “my way or the highway” style. A more acceptable means to reduce uncertainty is to seek more information through
testing. The past 2 decades have witnessed a proliferation of new cancer tests and improvements in older ones. Highly sensitive scans and molecular and genetic markers allow us to more accurately characterize risk for or extent of disease and response to treatment, reducing uncertainty in decision making. As the tests proliferated, questions arose whether more information is always a good thing. Magnetic resonance imaging for uncomplicated low back pain can lead to unnecessary surgery.\textsuperscript{7} After routine fetal monitoring was introduced, childbirth became a surgical procedure for a quarter of women.\textsuperscript{8} The dissemination of prostate-specific antigen screening was followed by an iatrogenic epidemic of prostate cancer. This is a difficult message to accept. How can more information possibly hurt? Avoiding information sounds antiscientific. Can we not still obtain the information but interpret it more wisely? A nice sentiment, but it lacks evidence of feasibility in real life. The analyses by Esselen et al\textsuperscript{1} suggest that information on increased CA-125 drove initiation of second line chemotherapy as rapidly after the report\textsuperscript{2,3} by Rustin as before. Another difficulty involves telling physicians that they may be doing the wrong thing. Whether it involves tests or treatments, it is no easy task to convince physicians that they are causing more harm than good. There are a number of predictable responses to reports such as the 1 by Rustin et al\textsuperscript{2,3} One is what I call the moving target. “Okay, so that surgery (or radiotherapy or whatever) had bad outcomes, but you don’t understand that the techniques have improved dramatically since the time of your data.” Such a response has the advantage of sometimes being true. Other responses include questioning the patient selection: “Those aren’t the people I see in my practice” or the physicians studied: “No wonder it didn’t work. I don’t do it that way!” All 3 of these responses and more greeted the Rustin study.\textsuperscript{11,12} What did not occur was any change in practice. Readers might want to conduct a thought experiment to ask themselves: “What if the results reported for delayed treatment were found instead for a new chemotherapy regimen? How would the report have had an effect on practice?” The second set of reasons has to do with framing the results of the Rustin study. The 2 approaches studied by Ruskin et al\textsuperscript{2,3} were characterized as early vs delayed treatment, but that was not what they studied, at least not in my opinion. They were in essence comparing CA-125 surveillance every 3 months vs no testing. The “no testing” group received CA-125 testing, but since the results were not released to the physicians, it was the same as not testing. The findings of the study are then best framed as routine surveillance with CA-125 testing is harmful in patients diagnosed with ovarian cancer in remission after initial treatment. Another factor that impedes clear thinking about harmful tests and treatments is the injection of medical economics into the discussion. Discussions of cost-effectiveness can make clinicians uncomfortable. The results of cost-effectiveness analyses can vary widely depending on the assumptions. And why should physicians act as societal financial gatekeepers? It is difficult enough helping patients decide on what is best for them without introducing the concept of what is best for society. In addition, such discussions can be seen by our patients as attempts at rationing their care. The suspicion that other patients, perhaps those with better insurance or better connections, might be receiving better treatment can destroy trust in the physician. But in the context of CA-125 testing, the issue of cost-effectiveness becomes absurd. How can a test or treatment be cost-effective if it is not effective —indeed, if it is harmful? Thus, I am uncomfortable with the focus on the economic impact of continued CA-125 testing by Esselen et al.\textsuperscript{1} It is not by any means irrelevant, but it muddies the issue. Once again, the findings of the Ruskin study are that routine surveillance testing is harmful. That should be the focus for subsequent decisions by clinicians, payers, and policy makers—not the costs involved. And, of course, the women with ovarian cancer contribute to the decisions to obtain C-125 testing. While physicians may be challenged dealing with uncertainty, many of our patients refuse absolutely to tolerate it. They want to know, even if that knowledge can lead to harm. Thus, in a shared decision making context, most patients will choose more information.\textsuperscript{13} But why would clinicians present the option of CA-125 testing? Shared decision making does not require that physicians present the patient with harmful options. We do not discuss heart transplants with patients who have mild congestive heart failure. Why would we discuss CA-125 testing with women who have ovarian cancer in remission? Will the practice of obtaining routine CA-125 testing change? I doubt it. The moving target argument is too strong. There will be better tests, and more effective treatments. And studies like that of Ruskin with uncomfortable results are usually not replicated.\textsuperscript{14} The issue is allowed to fade away. The fatal attraction of more information is too compelling.

Use of CA-125 Tests and Computed Tomographic Scans for Surveillance in Ovarian Cancer.
http://jamanetwork.com.ezproxy.uky.edu/journals/jamaoncology/fullarticle/2536203

Key Points

Question Did a 2009 randomized clinical trial demonstrating that cancer antigen 125 (CA-125) tests for routine surveillance in ovarian cancer increase use of chemotherapy and decreased patients’ quality of life without improving overall survival change current use of these tests?

Findings In this multi-institutional prospective cohort study of women diagnosed with ovarian cancer from 2004 to 2011, there was no change in the use of CA-125 tests or computed tomographic scans following the 2009 randomized clinical trial.

Meaning CA-125 tests and CT scans are still routinely used for surveillance testing in ovarian cancer without proven benefit.
Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations


http://jamanetwork.com.ezproxy.uky.edu/journals/jamaoncology/fullarticle/2531470

Key Points

Question Are women with BRCA mutations who undergo risk-reducing salpingo-oophorectomy (RRSO) without hysterectomy at increased risk for uterine cancer compared with expected rates from the Surveillance, Epidemiology, and End Results database?

Findings In this prospective cohort study, no increased risk for endometrioid carcinoma or sarcoma was seen. During a median 5.1 years of follow-up, 4 serous and/or serous-like carcinomas were seen in 627 women with BRCA1 mutations vs 0.18 expected (observed to expected ratio, 22.2), a significant difference.

Meaning Women with BRCA1 mutations have an increased risk for serous and/or serous-like endometrial cancer that should be considered when discussing advantages and risks of hysterectomy at the time of RRSO.

Abstract

Importance The link between BRCA mutations and uterine cancer is unclear. Therefore, although risk-reducing salpingo-oophorectomy (RRSO) is standard treatment among women with BRCA mutations (BRCA+ women), the role of concomitant hysterectomy is controversial.

Objective To determine the risk for uterine cancer and distribution of specific histologic subtypes in BRCA+ women after RRSO without hysterectomy.

Design, Setting, and Participants This multicenter prospective cohort study included 1083 women with a deleterious BRCA1 or BRCA2 mutation identified from January 1, 1995, to December 31, 2011, at 9 academic medical centers in the United States and the United Kingdom who underwent RRSO without a prior or concomitant hysterectomy. Of these, 627 participants were BRCA1+; 453, BRCA2+; and 3, both. Participants were prospectively followed up for a median 5.1 (interquartile range [IQR], 3.0-8.4) years after ascertainment, BRCA testing, or RRSO (whichever occurred last). Followup data available through October 14, 2014, were included in the analyses. Censoring occurred at uterine cancer diagnosis, hysterectomy, last follow-up, or death. New cancers were categorized by histologic subtype, and available tumors were analyzed for loss of the wild-type BRCA gene and/or protein expression.

Main Outcomes and Measures Incidence of uterine corpus cancer in BRCA+ women who underwent RRSO without hysterectomy compared with rates expected from the Surveillance, Epidemiology, and End Results database.
Among the 1083 women women who underwent RRSO without hysterectomy at a median age 45.6 (IQR: 40.9 - 52.5), 8 incident uterine cancers were observed (4.3 expected; observed to expected [O:E] ratio, 1.9; 95% CI, 0.8-3.7; P = .09). No increased risk for endometrioid endometrial carcinoma or sarcoma was found after stratifying by subtype. Five serous and/or serous-like (serous/serous-like) endometrial carcinomas were observed (4 BRCA1+ and 1 BRCA2+) 7.2 to 12.9 years after RRSO (BRCA1: 0.18 expected [O:E ratio, 22.2; 95% CI, 6.1-56.9; P < .001]; BRCA2: 0.16 expected [O:E ratio, 6.4; 95% CI, 0.2-35.5; P = .15]). Tumor analyses confirmed loss of the wild-type BRCA1 gene and/or protein expression in all 3 available serous/serous-like BRCA1+ tumors.

Conclusions and Relevance Although the overall risk for uterine cancer after RRSO was not increased, the risk for serous/serous-like endometrial carcinoma was increased in BRCA1+ women. This risk should be considered when discussing the advantages and risks of hysterectomy at the time of RRSO in BRCA1+ women.

Does the Number of Neoadjuvant Chemotherapy Cycles before Interval Debunking Surgery Influence Survival in Advanced Ovarian Cancer?


Objective: To evaluate the overall survival (OS) of patients with initially inoperable advanced ovarian cancer, tubal carcinoma, or primary peritoneal carcinoma of stages III or IV undergoing neoadjuvant chemotherapy (NAC) followed by cytoreductive surgery, according to the number of cycles performed.

Methods: This retrospective study was conducted in three main oncology centres in the east of France, reviewing the charts of all patients who underwent NAC between January 1, 1998 and October 31, 2012. We performed an OS analysis using multivariate Cox regression models adjusted for potential confounders. We also analysed progression-free survival (PFS) as well as chemotherapy- and surgery-related morbidity.

Results: Of the 204 patients included, 75 (36.8%) underwent ≤4 NAC cycles and 129 (63.2%) ≥5 NAC cycles. Characteristic data were similar in the two groups. Five-year OS was 35.0 and 25.8%, respectively. This difference was non-significant [HR = 1.06 (0.70-1.59), p = 0.79]. We also found no differences in PFS or morbidity between the two groups.

Conclusions: The number of NAC cycles does not seem to play a role in the OS of patients with advanced ovarian cancer. Further evidence and prospective data are needed to assess the value of a high/low number of NAC cycles among these patients.

November


The American Society of Clinical Oncology (ASCO) and the Society of Gynecologic Oncology (SGO) have together developed clinical practice guidelines for treating advanced-stage ovarian cancer. The guidelines help society members decide whether to use neoadjuvant chemotherapy (NACT) as a first step to chemically reduce tumor size, or primary cytoreductive surgery (PCS) to remove the bulk of a tumor before chemotherapy. “It was an important collaboration since it tackled a highly controversial area,” said Mitchell Edelson, M.D., cochair and SGO’s representative on the expert panel that developed the guidelines. “Bringing the two groups together to tackle this issue gets the word out to both memberships, which encompass a large number of physicians that take care of women with gynecologic cancers. The new recommendations could affect the treatment regimen that most women with ovarian cancer receive. According to the International Federation of Gynecology and Obstetrics, nearly 75% of women with epithelial ovarian cancer present with stages IIIC and IV disease. “I’ve been hoping for guidelines like these to come out for some time. I think they’re appropriate and hope that we’ll see more NACT in this country. Until now, it has been more of a European thing and hasn’t caught on in this country.” Whether to prescribe NACT or PCS has been controversial. Until now, treatment with primary PCS followed by chemotherapy has been the standard of care for advanced disease. “For years we believed that any woman diagnosed with advanced ovarian cancer should have surgery before chemotherapy,” said Alexi Wright, M.D., M.P.H., assistant professor of medicine at Harvard Medical School and a researcher at Dana–Farber Cancer Institute in Boston. “However, recent randomized clinical trials compared PCS and chemotherapy to NACT followed by interval cytoreductive surgery and adjuvant chemotherapy for women with advanced ovarian cancer,” and the researchers reported that, with respect to progression-free and overall survival, NACT was sometimes as effective as PCS—and caused less treatment-related morbidity and mortality. “Still, many American physicians doubted the findings and others ignored them,” Wright said. “With these guidelines we’ve clarified that women with stage IV ovarian cancer should receive chemotherapy before surgery, but women with stage III disease who have a high likelihood of having a complete cytoreduction—reducing the number of cancer cells to no visible disease—should have surgery first if it is safe.” Wright served as cochair and ASCO’s representative on the expert panel that developed the new standards. The guidelines appeared in the Aug. 8, 2016, issues of Gynecologic Oncology and the Journal of Clinical Oncology. A multidisciplinary panel with expertise in gynecologic oncology and medical oncology developed the list. The panel also included a patient.
advocacy representative. The panel reviewed literature published between March 20, 2005, and March 20, 2015, with the primary evidence forming the recommendations derived from four phase III clinical trials. The panel’s key recommendations include the following:

- Evaluating all women with suspected stage IIIC or IV invasive epithelial ovarian cancer before starting chemotherapy to determine whether they are candidates for PCS
- Offering NACT to all women at high risk or who are unlikely to achieve cytoreduction
- ASCO’s membership includes more than 40,000 oncology professionals. SGO has 2,000 members, including primarily gynecologic oncologists as well as allied health care professionals involved in treating and caring for women with cancer.

“The collaboration is significant because if either group had done this alone, it would be easy to argue that the guidelines were biased,” Wright said.

Many oncology professionals, including Gary Leiserowitz, M.D., belong to both organizations. Leiserowitz is professor and chair of the department of obstetrics and gynecology and chief of the division of gynecologic oncology at UC Davis Health System in Davis, Calif. He said he was impressed with the makeup of the committee: “It includes several people who have been strong proponents and champions of primary surgery for ovarian cancer. So it lends weight to the views that in the right setting, use of NACT is a completely reasonable alternative to primary debulking surgery.” William McGuire, M.D., professor of internal medicine at Massey Cancer Center at Virginia Commonwealth University School of Medicine in Richmond, said he is pleased overall with the committee’s recommendations. “I’ve been hoping for guidelines like these to come out for some time. I think they’re appropriate and hope that we’ll see more NACT in this country. Until now, it has been more of a European thing and hasn’t caught on in this country.” Edelson said the guidelines will be amended when warranted: “The panel discussed a number of other interesting areas of research in this field that needs to be tackled, and also point out a need for more clinical trials related to this topic.” Edelson and others point out that the new recommendations are just guidelines; individuals are free to follow them or not. Doctors and patients may decide on different treatment options given specific cases. “While on the whole I think the guidelines are good, most people who do this for a living and have high volumes of ovarian cancer patients have probably come to their own conclusions,” said Thomas Herzog, M.D., clinical director of the Barrett Cancer Center and chair of the University of Cincinnati Cancer Institute in Ohio. “For them I don’t know if this is going to be all that illuminating, but for those who don’t do this on a daily basis I think that this is going to be helpful in terms of clarifying the literature and sort of giving some direction as to where to go with advanced-stage ovarian cancer patients.” McGuire said that the recommendations won’t persuade everyone to change current practices.

“There’s still going to be the long time PCS surgeons who are in favor of surgery that takes 8–10 hours. People like that are dyed in the wool, and they’re going to continue to operate, operate, and operate some more.”


Abstract

The histopathologic features of adult granulosa cell tumors (AGCTs) are relatively nonspecific, resulting in misdiagnosis of other cancers as AGCT, a problem that has not been well characterized. FOXL2 mutation testing was used to stratify 336 AGCTs from three European centers into three categories: 1) FOXL2 mutant molecularly defined AGCT (MD-AGCT) (n = 256 of 336), 2) FOXL2 wild-type AGCT (n = 17 of 336), 3) misdiagnosed other tumor types (n = 63 of 336). All statistical tests were two-sided. The overall and disease-specific survival of the misdiagnosed cases was lower than in the MD-AGCTs (P < .001). The misdiagnosed cases accounted for 71.9% of disease-specific deaths within five years. In the population-based cohort, overall survival of MD-AGCT patients was not different from age-matched, population-based controls. Even though 35.2% of all the MD-AGCT patients in our study experienced a relapse, AGCT is usually an indolent disease. The historical, premolecular data underpinning our clinical understanding of AGCT was likely skewed by inclusion of misdiagnosed cases, and future management strategies should reflect the potential for surgical cure and long survival even after relapse.


The recently reported association of K3326X variant with the risk of developing breast and ovarian cancers independently of other pathogenic variants in BRCA2 (1) presents three major clinical issues: 1) the indication for cascade family screening and related monitoring decisions in relatives who carry the variant; 2) the role of the variant in decision-making (risk-reducing surgery) in affected carrier patients; 3) the potential use of poly(ADP-ribose) polymerase (PARP) inhibitors in K3326X carriers with platinum-sensitive, relapsed serous ovarian cancer. The clinical relevance of the data reported by Meeks and coauthors (1) may impact the clinical management of patients and families. According to major BRCA mutation databases (https://research.nhgrl.nih.gov/projects/bic/), the K3326X truncation-predicting variant (rs11571833) does not carry clinical importance and there are no functional data supporting its potential importance.
pathologic role; with “301 # of times recorded” through September 24, 2015, this variant is still clinically classified in the pending category. We, and other breast cancer units worldwide, systematically consult existing databases before releasing and signing genetic reports and use reported data as reference for interpretation of genetic findings. In a consecutive series of 755 probands with hereditary breast and ovarian cancer (HBOC), which we systematically analyzed by sequencing and Multiplex ligation-dependent probe amplification (MLPA) both BRCA1 and BRCA2 genes, we identified 103 pathologic mutations in BRCA1 and 111 in BRCA2 (28.3%), including four major rearrangements. In an additional 13 probands, we identified the K3326X variant that was associated with a mutation in only one case (BRCA1 p.Thr1677_Asn1678fs). We managed the information about the K3326X variant as for other variants of uncertain significance; we did not suggest cascade genetic family screening, with the exception of the proband that carried both p.Thr1677_Asn1678fs in BRCA1 and K3326X in BRCA2. Now, after publication of these new data, we are going to propose further counseling to inform patients about the novel risk estimate and the possibility of performing family cascade genetic testing. Correspondingly, we have to manage decisions on treatment in platinum-sensitive, relapsed serous ovarian cancer: Given the prior interpretation of the K3326X as VUS, we did not consider this variant a criterion for treatment with PARP inhibitor. Finally, indication to preventive surgery in carriers of the K3326X remains to be established. The way of informing patients, however, is now a major issue to be managed by the clinical community: Should we now deal with K3326X as we do other certain pathologic mutations, or should we advise caution in transmitting information about risk? While congratulating the authors for their valuable contribution, we would appreciate knowing their opinion and the modifications done in their clinical work-plans. Suggestions, if not precise indications, would help all breast and ovarian cancer units to manage appropriate information, family screening, and clinical decisions.

October 2016
CRISPR/Cas9-Mediated Trp53 and Brca2 Knockout to Generate Improved Murine Models of Ovarian High-Grade Serous Carcinoma.  J Walton, J Blagih, D Ennis, E Leung, S Dowson, M Farquharson, LA Tookman, C Orange, D Athineos, S Mason, D Stevenson, K Blyth, D Strathdee, FR Balkwill, K Vousden, M Lockley and IA McNeish Cancer Res. 76(20); 6118–29 DOI: 10.1158/0008-5472.CAN-16-1272 Published 15 October 2016 http://cancerres.aacrjournals.org/content/76/20/6118
There is a need for transplantable murine models of ovarian high-grade serous carcinoma (HGSC) with regard to mutations in the human disease to assist investigations of the relationships between tumor genotype, chemotherapy response, and immune microenvironment. In addressing this need, we performed whole-exome sequencing of ID8, the most widely used transplantable model of ovarian cancer, covering 194,000 exomes at a mean depth of 400× with 90% exons sequenced >50×. We found no functional mutations in genes characteristic of HGSC (Trp53, Brca1, Brca2, Nf1, and Rb1), and p53 remained transcriptionally active. Homologous recombination in ID8 remained intact in functional assays. Further, we found no mutations typical of clear cell carcinoma (Arid1a, Pik3ca), low-grade serous carcinoma (Braf), endometrioid (Ctnnb1), or mucinous (Kras) carcinomas. Using CRISPR/Cas9 gene editing, we modeled HGSC by generating novel ID8 derivatives that harbored single (Trp53−/−) or double (Trp53−/−;Brca2−/−) suppressor gene deletions. In these mutants, loss of p53 alone was sufficient to increase the growth rate of orthotopic tumors with significant effects observed on the immune microenvironment. Specifically, p53 loss increased expression of the myeloid attractant CCL2 and promoted the infiltration of immunosuppressive myeloid cell populations into primary tumors and their ascites. In Trp53−/−;Brca2−/− mutant cells, we documented a relative increase in sensitivity to the PARP inhibitor rucaparib and slower orthotopic tumor growth compared with Trp53−/− cells, with an appearance of intratumoral tertiary lymphoid structures rich in CD3+ T cells. This work validates new CRISPR-generated models of HGSC to investigate its biology and promote mechanism-based therapeutics discovery.

Commentary on microRNA Fingerprint in Human Epithelial Ovarian Cancer.  MV Iorio and CM Croce DOI: 10.1158/0008-5472.CAN-16-2637 Published 1 November 2016 http://cancerres.aacrjournals.org/content/76/21/6143
The highlighted article (Cancer Res 2007;67(18):8699–707) described for the first time the miRNA aberrant expression in human epithelial ovarian cancer. Along with the miRNA profiling we performed in human breast cancer a couple of years earlier, it represents a pioneer study in the field of miRNAs and one of the first reports describing the involvement of these small noncoding RNA molecules in solid tumors. MiRNAs underwent a long period of silence after their initial discovery back in 1993 by Victor Ambros as molecules playing a crucial role in the development of the nematode Caenorhabditis elegans, approximatively 10 years, during which the interest of scientists stuck to the existing knowledge on coding genes, until the first years of this century, when Dr. Croce's team described for the first time the loss of the locus encoding two miRNAs, miR-15a and miR-16-2, mapping at 13q14, in chronic lymphocytic leukemia. His post-docs had spent years (and tears) searching for a nonexistent gene uncoding an oncosuppressive protein in that area of the genome. None. This evidence was a breakthrough discovery, which literally changed the dogma of the “DNA—mRNA—protein” axis. Not only are small noncoding RNA molecules not junk RNA, but they represent the large majority of the information hidden in the sequence of human genome. We now realize that looking only at the coding sequences was like reading only the titles of the chapters of an entire book. In our study on human epithelial ovarian cancer, miRNA signatures were also able to
Discriminate among different tumor subgroups, providing an extremely important message, afterward applied to different human neoplasms. These small noncoding RNA molecules are not only altered in neoplastic cells in comparison with the corresponding normal tissue, but they also have potential as diagnostic biomarkers. Moreover, many of the miRNAs described in our original study have been later validated and investigated for a functional involvement in the occurrence and/or progression of ovarian cancer. Indeed, our data have been confirmed for the most part, although the normal tissue we used as control in our study was not optimal, as we extracted RNA from the total ovary, where the percentage of epithelial cells, the cellular type originating the neoplasia, is limited. We found miR-141, miR-200a, miR-200b, and miR-200c to be overexpressed in carcinomas and miR-125b1, miR-140, miR-145, and miR-199a to be downregulated. MiR-140, for instance, is located on chromosome 6q22, which is often deleted in ovarian tumors, and this miRNA is thought to target genes associated with invasion, including matrix metalloproteinase 13, FGF 2, and angiogenic VEGFA. Independent studies have confirmed a global downregulation of miRNA expression in advanced tumors (2), evidence that might explain the association of reduced levels of DICER and DROSHA, major enzymes responsible for miRNA processing, with poor prognosis in human ovarian cancer.

**Ovarian Cancer Chemoresistance Relies on the Stem Cell Reprogramming Factor PBX1.** J-G Jung, I-M Shih, JT Park, E Gerry, TH Kim, A Ayhan, K Handschuh, B Davidson, AN Fader, L Selleri and T-L Wang. Cancer Res; 76(21); 6351–61, 2016 [http://cancerres.aacrjournals.org/content/76/21/6351](http://cancerres.aacrjournals.org/content/76/21/6351)

The evolution of chemoresistance is a fundamental characteristic of cancer that ultimately hampers its clinical management. However, it may be possible to improve patient outcomes significantly by a better understanding of resistance mechanisms, which cancers rely upon during the evolution to an untreatable state. Here we report an essential role of the stem cell reprogramming factor, PBX1, in mediating chemoresistance in ovarian carcinomas. In the clinical setting, high levels of PBX1 expression correlated with shorter survival in post-chemotherapy ovarian cancer patients. In tumor cells with low endogenous levels of PBX1, its enforced expression promoted cancer stem cell-like phenotypes, including most notably an increase in resistance to platinum-based therapy used most commonly for treating this disease. Conversely, silencing PBX1 in platinum-resistant cells that overexpressed PBX1 sensitized them to platinum treatment and reduced their stem-like properties. An analysis of published genome-wide chromatin immunoprecipitation data indicated that PBX1 binds directly to promoters of genes involved in stem cell maintenance and the response to tissue injury. We confirmed direct regulation of one of these genes, STAT3, demonstrating that the PBX1 binding motif at its promoter acted to positively regulate STAT3 transcription. We further demonstrated that a STAT3/JAK2 inhibitor could potently sensitize platinum-resistant cells to carboplatin and suppress their growth in vivo. Our findings offer a mechanistic rationale to target the PBX1/STAT3 axis to antagonize a key mechanism of chemoresistance in ovarian cancers and possibly other human cancers.


**Abstract** Carcinosarcomas (CSs) of the uterus and ovary are highly aggressive neoplasms containing both carcinomatous and sarcomatous elements. We analyzed the mutational landscape of 68 uterine and ovarian CSs by whole-exome sequencing. We also performed multiregion whole-exome sequencing comprising two carcinoma and sarcoma samples from six tumors to resolve their evolutionary histories. The results demonstrated that carcinomatous and sarcomatous elements derive from a common precursor having mutations typical of carcinomas. In addition to mutations in cancer genes previously identified in uterine and ovarian carcinomas such as TP53, PIK3CA, PPP2R1A, KRAS, PTEN, CHD4, and BCOR, we found an excess of mutations in genes encoding histone H2A and H2B, as well as significant amplification of the segment of chromosome 6p harboring the histone gene cluster containing these genes. We also found frequent deletions of the genes TP53 and MBD3 (a member with CHD4 of the nucleosome remodeling deacetylase complex) and frequent amplification of chromosome segments containing the genes PIK3CA, TERT, and MYC. Stable transgenic expression of H2A and H2B in a uterine serous carcinoma cell line demonstrated that mutant, but not wild-type, histones increased expression of markers of epithelial–mesenchymal transition (EMT) as well as tumor migratory and invasive properties, suggesting a role in sarcomatous transformation. Comparison of the phylogenetic relationships of carcinomatous and sarcomatous elements of the same tumors demonstrated separate lineages leading to these two components. These findings define the genetic landscape of CSs and suggest therapeutic targets for these highly aggressive neoplasms.

**Significance** Some cancers, termed carcinosarcomas (CSs), have mixed cell types, with either epithelial or mesenchymal features. Sequencing the genomes of uterine and ovarian CSs demonstrated that these different cell types derive from a common precursor cell that has many mutations typical of epithelial cancers. In addition, we find that these tumors have a significant burden of point mutations and amplification of histone genes, suggesting a potential role of
Is Ovarian Cancer Managed According to Clinical Guidelines? Evidence From a Population-Based Clinical Audit. Sobrero, S; Pagano, E; Piovano, E; Bono, L; Ceccarelli, M; Ferrero, A; Macchi, C; Mistrangelo, M; Patriarca, S; Tripodi, E; Zanetti, R; Bertetto, O; Ciccone, G; Zola, P. International Journal of Gynecological Cancer

Patients and Methods: Residents diagnosed with OC in 2009 were identified in the regional hospital discharge records database. All hospitalizations within 2 years from diagnosis were reviewed. Patients were classified according to their initial pattern of care, defined as “with curative intent” (CIPC) if including debulking surgery aimed at maximal cytoreduction. Adherence to guidelines for surgery and chemotherapy and the effects of this adherence on OC survival were investigated with logistic regression and Cox models.

Results: The final study sample consisted of 344 patients with OC, 215 (62.5%) of whom received CIPC. Increasing age, comorbidities, and metastases were negatively associated with receiving CIPC. In the CIPC group, surgical treatment was adherent to guidelines in 35.2%, whereas chemotherapy was adherent in 87.8%. Surgical treatment that was adherent to guidelines [hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.45–1.15] and absence of residual tumor (HR, 0.55; 95% CI, 0.32–0.94) were associated with better survival in the CIPC group, and chemotherapy that was adherent to guidelines was associated with a significant reduction in the risk of death (HR, 0.49; 95% CI, 0.28–0.87).

Conclusions: Results support the need to reorganize the clinical pathway of patients with OC in the Piedmont Region and the need for better adherence to current guidelines.

Common STD May Have Come from Neanderthals: Cross-species trysts likely spread human papillomavirus (HPV) to Homo sapiens, according to new research. B Grant The Scientist October 20, 2016 http://www.the-scientist.com/?articles.view/articleNo/47308/title/Common-STD-May-Have-Come-from-Neanderthals&utm_campaign=NEWSLETTER_TS_The-Scientist-Daily_2016&utm_source=hs_email&utm_medium=email&utm_content=36178340&_hsenc=p2ANqtz-_TFRJCC5p5cdaWMfFOYiJDSqRudvtLg-HtoaqZeSkJwApzglR4J6dNuFzoPlm8R-OaY1uwADHve5bvy222Kkybndwrfq&_hsml=36178340

Researchers have already established that early Homo sapiens and Neanderthals interbred at some point in our shared evolutionary history. Those cross-species rendezvous are the reason why the DNA of non-Africans contains somewhere between one percent and five percent Neanderthal genomic material. Now, scientists claim that Neanderthals gave our ancestors not just DNA, but a sexually transmitted disease as well. Reporting their findings earlier this month in Molecular Biology and Evolution, researchers from Spanish, Brazilian, and French institutions claim that the human papillomavirus HPV16 strain, which infects about four percent of Americans and can lead to cervical cancer, is about 500,000 years old and likely originated in Neanderthal populations or in Denisovans, another extinct human ancestor. “Oncogenic viruses are very ancient,” Ignacio Bravo of the French National Center for Scientific Research told Laboratory Equipment. “The history of humans is also the history of the viruses we carry and we inherit. Our work suggests that some aggressive oncogenic viruses were transmitted by sexual contact from archaic to modern humans.” Bravo and his colleagues obtained 118 full sequences of HPV16 from five different subtypes to assemble a genetic timeline that suggested the transmission of that strain went from Neanderthals or Denisovans to Homo sapiens. And the current prevalence of HPV16 corroborates that suggestion. The strain is virtually absent from Sub-Saharan African people, meaning that humans who migrated out of Africa more than 100,000 years ago must have picked up the strain from elsewhere. See http://mbe.oxfordjournals.org/content/early/2016/10/05/molbev.msw214.short


Background: Current US cervical cancer screening guidelines do not differentiate recommendations based on a woman’s human papillomavirus (HPV) vaccination status. Changes to cervical cancer screening policies in HPV-vaccinated women should be evaluated.

Methods: We utilized an individual-based mathematical model of HPV and cervical cancer in US women to project the health benefits, costs, and harms associated with screening strategies in women vaccinated with the bivalent,
quadrivalent, or nonavalent vaccine. Strategies varied by the primary screening test, including cytology, HPV, and combined cytology and HPV “cotesting”; age of screening initiation and/or switching to a new test; and interval between routine screens. Cost-effectiveness analysis was conducted from the societal perspective to identify screening strategies that would be considered good value for money according to thresholds of $50 000 to $200 000 per quality-adjusted life-year (QALY) gained.

**Results:** Among women fully vaccinated with the bivalent or quadrivalent vaccine, optimal screening strategies involved either cytology or HPV testing alone every five years starting at age 25 or 30 years, with cost-effectiveness ratios ranging from $34 680 to $138 560 per QALY gained. Screening earlier or more frequently was either not cost-effective or associated with exceedingly high cost-effectiveness ratios. In women vaccinated with the nonavalent vaccine, only primary HPV testing was efficient, involving decreased frequency (ie, every 10 years) starting at either age 35 years ($40 210 per QALY) or age 30 years ($127 010 per QALY); with lower nonavalent vaccine efficacy, 10-year HPV testing starting at earlier ages of 25 or 30 years was optimal. Importantly, current US guidelines for screening were inefficient in HPV-vaccinated women.

**Conclusions:** This model-based analysis suggests screening can be modified to start at later ages, occur at decreased frequency, and involve primary HPV testing in HPV-vaccinated women, providing more health benefit at lower harms and costs than current screening guidelines. ASCO Resource-Stratified Guidelines: http://ascopubs.org/doi/pdf/10.1200/JGO.2016.006577

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**September 2016**


For decades, U.S. policymakers have tried to offer health insurance to the entire country. Although politicians made progress, through Medicare and Medicaid and most recently through the Affordable Care Act (ACA), the main goal continues to be elusive. The ACA implemented reforms designed to improve the accessibility, affordability, and quality of health care. Last April, health care experts convened for a panel discussion at the annual meeting of the American Association for Cancer Research of how the law affects cancer research and treatment. Their assessments were mixed. Although the ACA has improved access to cancer treatment, prevention services, and clinical trials, they agreed, it has done so unevenly, and many people still grapple with insufficient coverage. “The ACA is taking us in a positive direction,” said panelist Ernest Hawk, M.D., M.P.H., vice president for cancer prevention at the University of Texas M. D. Anderson Cancer Center in Houston, “but it hasn’t gone far enough in addressing the needs especially of poor and underserved people with cancer who have either no or limited health insurance.” Panel moderator Gil Omenn, M.D., Ph.D., director of the Center for Computational Medicine and Bioinformatics at the University of Michigan in Ann Arbor, credited the ACA with boosting preventive services, as illustrated by more people getting screened for colon, cervical, breast, and other cancers. Hawk cited government statistics indicating that 137 million Americans had access to preventive-services coverage without cost sharing in 2015, compared with only 71 million before the law. “The ACA is taking us in a positive direction, but it hasn’t gone far enough in addressing the needs especially of poor and underserved people with cancer who have either no or limited health insurance.” That’s a tremendous improvement,” he said. Hawk singled out improvements in rates of cervical cancer screening and human papillomavirus vaccination among women aged 19–25 years who receive dependent insurance coverage from their parents. Rates of early-stage cervical cancer diagnoses and fertility-sparing treatments had both increased for this age group, he said. Moreover, 1.1 million additional women had begun the human papillomavirus vaccination series and 840,000 additional women had completed it. But Hawk noted that cancer screening rates are also lower in the 19 states that declined Medicaid expansion under the ACA. Specifically, the odds of receiving mammograms and Pap smears are 13% lower in those states, he said, with the differences most pronounced among uninsured women. William Dalton, M.D., Ph.D., chief executive officer at M2Gen, a biotechnology company in Tampa, Fla. highlighted access disparities in clinical trials. The ACA prohibits insurance companies from dropping or denying coverage for patients who participate in clinical trials at in-network facilities. In addition, it requires insurers to cover routine costs of care. But in practice, Dalton said, insurers commonly deny coverage in clinical-trial settings. He cited a recent survey showing that 63% of queried cancer centers had reported denials of insurance payments during clinical trials, specifically for standard-of-care services that patients would otherwise receive. Often, he added, insurance companies wouldn’t pay for the tests needed to determine eligibility, such as tests for genetic mutations targeted by experimental precision treatments. “So we still have a ways to go, and ambiguities in the law need to be addressed, since they’re frankly being used by insurance companies for insurance denials,” Dalton said. Panelists also highlighted the growing role of comparative-effectiveness research under the ACA. The law created a new funding entity, the Patient Centered Outcomes Research Institute (PCORI), specifically to support studies that compare performance among approved treatments. PCORI-funded studies investigate, for instance, different ways to manage low-risk prostate cancers that might never be lethal during a man’s lifetime, or which type of imaging technology works best to show small breast tumors. The goal of this research is to generate real-world observational data that inspire changes in

Rapid advances in the molecular characterization of tumors, including complete gene sequencing of multiple cancers in the Cancer Genome Project, have led to an increased understanding of the molecular pathways that underlie cancer. These genomic changes differentiate tumors from normal tissues, permitting targeted treatments for several types of tumor and thereby extending survival and improving patients’ quality of life. Examples include trastuzumab for human epidermal growth factor receptor type 2 (HER2)–expressing breast cancer 1 and vemurafenib for melanomas that express mutated BRAF.2 These drugs have become standards of care and are important components of cancer treatment. The genomic changes define groups of patients with cancer who can benefit from treatment, although for most patients with metastatic cancer, the duration of benefit is limited and is followed by drug resistance and cancer progression. Progress in molecular pathology studies and their decreasing cost, increasing speed, and more comprehensive evaluation (from gene sequencing to expression profiles and proteomics) have encouraged investment by funding bodies and cancer centers in personalized (or precision) cancer medicine. The concept underlying this research is that molecular analysis of a tumor in an individual patient will allow the selection of effective drugs to control that tumor and thereby prolong survival. This concept is appealing to patients and to foundations that support cancer research, and the molecular characterization of tumors is being marketed directly to patients, despite a lack of evidence of benefit.3 Here we critically review the problems that have been associated with personalized medicine in patients with cancer; we suggest that the clinical benefit of personalized medicine as it is currently practiced will be limited.

RESEARCH PROGRAMS There is a strong focus on personalized medicine by large cancer centers and those who fund research. In his State of the Union address, President Barack Obama announced that he had allocated $215 million in the 2016 U.S. budget for precision medicine, of which $70 million is allocated to the National Cancer Institute (NCI) to support research and clinical trials of personalized cancer medicine as part of the Cancer Moonshot Initiative.4 Almost all the 69 NCI-supported cancer centers have websites that emphasize programs in personalized medicine, although many centers advise patients that personalized medicine cannot yet be applied in the selection of treatments. Large, international cancer centers also have dedicated programs. Most institutions are pursuing independent research and clinical programs. Inevitably, different programs will document similar successes, limitations, and problems, which wastes resources, including patients to participate in well-designed trials, clinicians’ and scientists’ time, and money. Some groups have formed consortia, such as the Lung Cancer Mutation Consortium, which consists of 16 sites in the United States that are testing for driver mutations in multiple genes in metastatic adenocarcinoma of the lung, and the Stratification in Colorectal Cancer program in the United Kingdom,5 which has funding of £5 million (approximately $6.6 million U.S.) to provide genomic analysis for 2000 patients with colorectal cancer, but such collaborations are rare. The Cancer Moonshot Initiative from the U.S. government provides opportunities to boost collaboration. Ideally (and historically), different cancer institutions emphasize different avenues of research, so resources are applied to investigate multiple promising areas. Funding for research is finite, and the concentration of research on personalized medicine might deprive other promising avenues of research of appropriate resources (immunotherapy is an exception). A few large coordinated efforts are appropriate to determine whether personalized medicine might lead to substantial improvements in outcome, but it would be wasteful for 30 to 40 independent programs to study the same approach. CLINICAL STUDIES We are aware of one randomized trial that compared outcomes in patients who were treated with targeted drugs that had been selected to match the genetic sequence of their tumor with outcomes in patients who received standard care.6 We also know of three large series that evaluated feasibility and tumor response in persons with advanced adenocarcinoma of the lung or in practice. “PCORI was designed to fit a research niche that’s not typically addressed by the National Cancer Institute,” said Scott Ramsey, M.D., Ph.D., a physician and health economist at the Fred Hutchinson Cancer Research Center in Seattle.” Launched in 2010, PCORI’s investments into cancer research totaled $176.4 million as of July 2016. “Since the ACA, comparative-effectiveness research has broken into the broader consciousness of the cancer research community,” said Ethan Basch, M.D., professor of medicine and public health at the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill. “People who had never heard of it are now expressing interest.” But Basch pointed out that barriers remain. In particular, comparative-effectiveness studies require integrated electronic health records and other data collection platforms at different institutions so that information can be shared. “And though we’re making progress in this area, electronic health records are still too unstructured,” Basch said. “We need better ways to integrate patient outcomes with cancer registries. Without that, we can’t obtain a full picture of the patient experience.” Dalton said that there are “huge gaps in the development of health care informatics systems that we need to address through standardization and collaboration.” He added, “It comes down to questions of culture: How much information are we willing to share?” Omenn said that one of the benefits of the ACA is simply that it increased the ranks of the medically insured. “More attention to screening and prevention opens up new questions to investigate,” he added. “And potentially opens up a market of millions of people who can now afford to pay for their care.” But Hawk said challenges remain with meeting the needs of parts of the population that the ACA still can’t reach. “The biggest barrier to extending coverage to those subpopulations is fear,” he said. “Medicaid is a state and federal partnership. And when federal incentives for Medicaid expansion disappear, states will be left holding the financial bag. How we’re going to address that, I don’t know.”
women with breast cancer, whose treatment was selected on the basis of limited gene sequencing, and three large series that evaluated the feasibility of inclusion in trials or outcomes in large series of patients undergoing genetic testing at three cancer centers. The outcomes of these investigations are discouraging (Table 1). Although 30 to 50% of the patients who were referred for genetic analysis of their tumors had driver mutations that were thought to stimulate tumor progression (see below), only 3 to 13% had treatments that had been selected by individual genomic analysis. There was no between-group difference in outcome in the randomized trial, and a low proportion of the referred patients could be included in prospective trials or had any signal of benefit (<5%) in the single-group studies. Multiple factors may contribute to the limited success of the current clinical evaluation of personalized medicine, including limited access to targeted agents both within and outside clinical trials, as well as technical issues such as inadequate tumor specimens for analysis. Proponents point out correctly that molecular characterization will improve and that new and better drugs are likely to contribute to better results in future trials. However, we suggest that inherent limitations of molecular targeted agents, as well as the Darwinian evolution of tumors leading to intratumor heterogeneity, will limit this improvement.

MOLECULAR TARGETED AGENTS An increasing number of anticancer drugs are available that target different signaling pathways. They have two major limitations: most molecular targeted agents provide only partial inhibition of signaling pathways, and many are too toxic to be used in combination. Pathways that signal cell proliferation or cell survival in cancer cells are highly plastic and adaptable, whereas pathways that stimulate cell death may be suppressed. Normal cells depend on related signaling pathways, and their inhibition by molecular targeted agents leads to toxic effects. There have been major inconsistencies between preclinical studies seeking to validate molecular targets and the inhibition of these targets by candidate molecules, and the few references to achievable clinical levels of inhibition of the molecular target by these agents suggest that doses with an acceptable safety profile provide incomplete target inhibition.

The importance of molecular pathways is often specific to the cancer type. Several "basket" trials that are not based on histologic findings are ongoing in which patients with multiple types of cancer are recruited on the basis of an activated or mutated pathway. For example, vemurafenib was associated with a higher rate of survival than dacarbazine among patients with melanoma that expresses the BRAF V600E mutation but had only modest activity against other biomarker-selected cancers that express this mutation sporadically.

With the possible exception of immune-checkpoint inhibitors, cancer cells have an almost universal capacity to develop resistance to a single molecular targeted agent by means of up-regulation of the partially inhibited pathway, mutation of the target, or activation of alternative pathways. A combination of molecular targeted agents may inhibit alternative pathways, but the extent of signaling plasticity could render this approach impractical, because adaptive responses involve multiple other potential targets. Combinations of molecular targeted agents that target different pathways have often resulted in dose reduction because of toxic effects, thereby further reducing the inhibition of individual targets, and some combinations have been associated with unacceptable levels of side effects. In a review of 95 doublet combinations in 144 trials, approximately 50% of the combinations could use the full doses that were recommended for use as single agents, whereas other doublets required substantial dose reductions. There are few examples of successful combination of more than two molecular targeted agents, so even if cost were not a consideration, the use of multiple such agents in combination is usually not feasible.

TUMOR EVOLUTION AND INTRATUMOR HETEROGENEITY The molecular characterization of biopsy samples from different regions of multiple tumors in humans or from the primary tumor and metastases has shown substantial heterogeneity. Likewise, sequential biopsy samples from tumor sites in the same patient show considerable genomic heterogeneity. These findings have led to a Darwinian model of tumor evolution, which can be represented by a branching tree: some mutations are present in all sampled cancer cells and are clonal markers of the cancer, whereas others are unique to subclones that are generated. Sensitive genetic characterization of individual cancer cells indicates that intratumor heterogeneity is present early in cancer development and that subclones are selected by cancer treatment. Although many mutations may not influence proliferation or survival of the cancer cells (so-called passenger mutations), other acquired mutations (drivers) influence tumor progression and must be targeted in order for treatment to be effective. The development of intratumor heterogeneity poses major limits to the potential targeting of mutated pathways on the basis of molecular analysis of a tumor sample (i.e., limits to the central concept of personalized medicine). Molecular analysis of a single biopsy sample from a tumor does not represent other parts of it, and treatment that is based on that analysis, even if there is an effective agent, is likely to have limited benefit because molecular pathways that are active in other parts of the tumor will lead to tumor growth from different clones of tumor cells. Although the analysis of circulating tumor DNA (ctDNA) might mitigate the challenges of multiple biopsies, ctDNA may arise from subpopulations of a heterogeneous tumor, including dead cells, and the difficulty with regard to detecting minor, viable clones that are capable of repopulating a tumor after therapy remains. Treatment that leads to the death of drug-sensitive tumor cells might accelerate the emergence of resistant tumor cells, with tumor progression occurring largely by means of selection of preexisting tumor subclones. The failure to recognize the complexities of disease, of which intratumor heterogeneity is a prime example, is a key factor that is responsible for therapeutic failures (<10% of anticancer drugs that enter phase 1 clinical trials are approved for marketing) and the disparity between the level of investment in biomedicine and its output to improve human health.

The essential question for personalized cancer medicine is whether
any therapeutic strategy could provide cure or long-term remission despite the presence of intratumor heterogeneity. There are two possibilities. First, a clonal driver mutation might be present in all tumor cells and required for tumor progression despite other mutations in subclones, such that the inhibition of this pathway would lead to profound antitumor effects. Second, mutations that drive genomic instability and the development of intratumor heterogeneity could themselves be targeted. We think that successes from either approach are likely to be rare.

The successful treatment of chronic myeloid leukemia by imatinib is perhaps an example of such a clonal driver mutation, but it is an exception. The clonal BCR-ABL translocation is present in a high proportion of people with chronic myeloid leukemia and allows treatment of a group rather than an individual patient on the basis of the presence of a genetic biomarker. Responses of HER2-positive breast cancer to trastuzumab and BRAF-mutated melanoma to vemurafenib are probably due to driver mutations in all or almost all the tumor cells, but the emergence of drug resistance points to adaptation or selection of other driver mutations in subclones. The targeting of clonal markers that are present in all tumor cells by immunotherapy, rather than the inhibition of the pathways associated with them, is a potential approach. The concept of targeting genes that control genomic diversity is unlikely to succeed for the same reason that drugs that target the metastatic process are not useful: intratumor heterogeneity and micrometastases (in persons who will die from metastatic disease) will both be present by the time the tumor is diagnosed. Although the targeting of a DNA-repair gene in patients whose tumors have an existing mutation in a second DNA-repair gene can lead to tumor response, this effect is transient and is most likely due to the requirement of DNA repair for tumor-cell survival rather than to the inhibition of clonal diversity.

COST New drugs to treat cancer are marketed at ever-increasing prices, and unlike other commodities, price is unrelated to value (i.e., to clinical effectiveness). Expensive medications can be cost-effective (e.g., imatinib and trastuzumab), but the development and marketing of expensive drugs with marginal effectiveness diverts resources from the development of more effective therapies. The application of personalized medicine will involve substantial cost. Molecular analysis of tumor samples will become cheaper and more efficient, but the selection of multiple molecular targeted agents to treat tumors (concurrently or sequentially, depending on the presence of side effects) on the basis of aberrant pathways will be enormously expensive. This cost could be justified if the approach led to major gains in survival or its quality, but for the reasons we have expressed above, this situation is unlikely.

CONCLUSIONS The concept of personalized medicine is so appealing (see reviews by Biankin et al. and Swanton et al.) that seemingly only curmudgeons could criticize it. Learning more about the variability of the molecular characteristics of individual tumors and its relationship to the natural history and outcome of disease is important research but has not facilitated choice of treatment. We do not suggest abandoning personalized medicine but rather evaluating it in a small number of well-designed collaborative programs, with research programs that recognize and combat the limitations we have described. There should also be a clear message to patients that personalized cancer medicine has not led to gains in survival or its quality and is an appropriate strategy only within well-designed clinical trials.

Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline


Purpose To provide guidance to clinicians regarding the use of neoadjuvant chemotherapy and interval cytoreduction among women with stage IIIC or IV epithelial ovarian cancer.

Methods The Society of Gynecologic Oncology and the American Society of Clinical Oncology convened an Expert Panel and conducted a systematic review of the literature.

Results Four phase III clinical trials form the primary evidence base for the recommendations. The published studies suggest that for selected women with stage IIIC or IV epithelial ovarian cancer, neoadjuvant chemotherapy and interval cytoreduction are noninferior to primary cytoreduction and adjuvant chemotherapy with respect to overall and progression-free survival and are associated with less perioperative morbidity and mortality.

Recommendations All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy. The primary clinical evaluation should include a CT of the abdomen and pelvis, and chest imaging (CT preferred). Women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to < 1 cm of residual disease (ideally to no visible disease) should receive neoadjuvant chemotherapy. Women who are fit for primary cytoreductive surgery, and with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery. However, primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to < 1 cm (ideally to no visible disease) with acceptable morbidity. Before neoadjuvant chemotherapy is delivered, all patients should have confirmation of an invasive ovarian, fallopian tube, or peritoneal cancer. Additional information is available at www.asco.org/NACT-ovarian-guideline and www.asco.org/guidelineswiki

Reforms under the Affordable Care Act have reduced barriers to health care access by expanding insurance coverage to millions of individuals living in the United States. With primary barriers to access removed, secondary barriers, particularly related to transportation, have become increasingly important. In 2005, it was estimated that 3.6 million individuals failed to receive nonemergency medical care due to transportation barriers.1 These patients tended to be older, poorer, and ethnic or racial minorities. Patients with the highest burden of chronic disease typically have the greatest transportation barriers. Delays in treatment can cause chronic diseases to destabilize and progress, resulting in suboptimal outcomes and excessive use of resources.2,3 As a result, many payers ranging from the Centers for Medicare & Medicaid Services to state Medicaid programs to large commercial payers offer free or subsidized nonemergency medical transportation to beneficiaries. Nonemergency medical transportation services are provided by personnel who are not medically skilled and can include options spanning from wheelchair vans to car services. The nonemergency medical transportation benefits are most commonly available to populations with risk factors for both chronic disease and poor access to transportation. Federal regulations mandate that state Medicaid programs provide nonemergency medical transportation for qualifying beneficiaries, and in 2016 commercial Medicare Advantage plans offered nonemergency medical transportation benefits to 69.5% of all beneficiaries.4,5 The federal government spends an estimated $2.7 billion on nonemergency medical transportation annually, which is an amount expected to increase with expanded Medicaid enrollment. Many payers have embraced nonemergency medical transportation benefits because it makes sense to enable patients to receive necessary care. But current approaches to nonemergency medical transportation have numerous challenges. A recent Government Accountability Office report pointed to rising costs, program integrity, and vendor oversight as problems for federal payers. Patients also are not well served by the status quo—wait times routinely approach 60 minutes and drivers frequently do not show.4 Suboptimal service causes some patients to forgo treatment, the very outcome nonemergency medical transportation benefits were designed to prevent. In an analysis of 182,536 patients receiving dialysis, those who relied on car services were at an increased risk of missing hemodialysis treatments (odds ratio, 1.21; 95% CI, 1.16-1.25).3 There is a compelling need to provide reliable and efficient transportation services to the most vulnerable patients. Digital transportation network companies, such as Lyft and Uber, have revolutionized transportation services. Compared with taxis and livery services, digital transportation network companies offer improvements across dimensions ranging from cost to user experience.6 Several organizations have recently announced efforts to bring new transportation technologies to health care. In January, Lyft launched Concierge, a web-based product that allows organizations to request rides for customers through the Lyft platform. In April, Uber announced collaboration with a new company, Circulation, to fulfill third-party, health care–related ride requests. To pilot Concierge, Lyft has partnered with National MedTrans, a nonemergency medical transportation benefit manager. As part of the initial rollout, National MedTrans is offering the service to Medicaid enrollees in New York, New York, and to Medicare Advantage beneficiaries in California. The California pilot program involves CareMore, a network model health maintenance organization that operates Medicare Advantage plans. Most CareMore plans provide patients with nonemergency medical transportation benefits for preventive and chronic care services. Members arrange nonemergency medical transportation in advance (typically at least 24 hours but less if needed) by calling a dedicated telephone number. Previously, CareMore personnel would verify the request and the beneficiary’s benefits and then relay the request to a nonemergency medical transportation organization responsible for dispatching livery cars or vans. Under the pilot program, requests are transferred via a secure platform to National MedTrans, which uses Concierge to dispatch a Lyft driver to the specified location at the requested time. Early results from the pilot program are promising. Based on data from May 2016 to June 2016 involving 479 nonemergency medical transportation rides, average wait times have decreased by 30.0% (12.52 minutes to 8.77 minutes) and average per-ride costs have been reduced by 32.4% ($31.54 to $21.32). Composite patient measures yielded a satisfaction rate of 80.8%. Together, these outcomes underscore both the substantial opportunity to improve patient experience and lower costs, as well as the prospect for continued iteration and improvement. For example, some beneficiaries express confusion that Lyft vehicles are not branded with CareMore or other recognizable medical logos or that they are unsure exactly which type of car to look out for. As efforts such as Concierge and Circulation mature, larger, longer-term, controlled studies will be needed to accurately gauge the effect of these programs on access, costs, and experience. Notwithstanding the encouraging results from the pilot program, there are several unanswered questions and potential challenges surrounding the use of new technologies for nonemergency medical transportation. Decreasing barriers to access may increase the use of medical services, which, in the current era of cost sensitivity, could have unintended consequences. Putting aside the fact that getting patients to necessary treatment is imperative regardless of cost, there is reason to believe that the overall effect on use of care will be minor. Connecting patients with multiple chronic conditions to the care they need may actually reduce costs. A previous report from the National Academy of Sciences found that nonemergency medical transportation was cost-effective for most chronic conditions, and even saves costs for conditions such as congestive heart failure and diabetes. The same cluster of socioeconomic and demographic factors that create transportation barriers may also correlate with limited smartphone penetration—making digital transportation network companies difficult to access for vulnerable populations. Concierge is designed so that third parties can input information for users, obviating the need for a smartphone. Among population groups in whom smartphone penetration is higher, such as some Medicaid populations, beneficiaries may prefer to request rides directly. Relatedly, transportation network company penetration is clustered in urban centers, providing coverage to a large segment of the population, but leaving access sparse in rural areas. This points to the use of digital transportation network companies as
a complement to traditional nonemergency medical transportation approaches but not as an outright replacement. Traditional nonemergency medical transportation drivers do not have any medical training, but over time may develop experience transporting ill patients with special needs. Older, sicker patients may prefer a slower ride, or a helping hand in and out of the car, which are activities that are at odds with the financial incentives for transportation network company drivers. As these programs expand, it will be important to rigorously monitor patient experience and to provide this information to transportation network companies. CareMore is leveraging Lyft's driver communications programs to send notes and reminders to drivers before pick up about providing patient-centric service. Uber recently launched a new product, uberASSIST, in which drivers are specifically trained to assist seniors and those with disabilities. Digital transportation network companies have been apprehensive to enter the nonemergency medical transportation business because of concerns ranging from credentialing to information sharing to medical liability. For this reason, existing nonemergency medical transportation brokers, such as National MedTrans, are serving as conduits between the medical and transportation services worlds. With added experience, comfort, and infrastructure, direct collaborations are likely to develop. Digital transportation network companies have the potential to disrupt medical transportation, but the implications of this transformation extend beyond transportation. Observers have repeatedly highlighted the potential for new, disruptive technologies in health care, and have called for an “Uber for health care.” But many of the challenges standing in the way of effective and efficient health care (eg, excellent service, streamlined logistics) are not unique to the health care industry. Instead of waiting for the next big health care app, substantial advances could be made by integrating technologies that have already solved discrete problems shared by other fields. Lofty ambitions are important, but they can sometimes obscure viable solutions.


**Background** High-volume center surgery and gynecologic oncology care are associated with improved outcomes for women with uterine cancer. Referral patterns, from biopsy through to chemotherapy, may have patients interacting with high-volume centers for all, a portion, or none of their care. The relative frequency, the underlying factors that contribute to referral, and the potential impact of these referral patterns on treatment outcomes are unknown.

**Objective** We sought to analyze the referral patterns and subsequent impact of care sites on treatment for women with high- and low-risk uterine cancer.

**Study Design** This is a population-based retrospective cohort study of uterine cancer cases from 2004 through 2009 in North Carolina. Using state cancer registry files linked to Medicare, Medicaid, and private payer insurance claims, we analyzed referral and treatment patterns by annual surgical volume (high ≥12/y). We examined clinical and demographic factors associated with referral and used modified Poisson regression to evaluate risk of referral, lymphadenectomy, and chemotherapy. Stratified Kaplan-Meier plots and Cox proportional hazard models were used to examine survival.

**Results** A total of 2053 women were analyzed, including 34% (n = 677) with grade 3 histology. Of 1630 (80%) women with preoperative biopsies, referral patterns (biopsy to surgery) were: low volume to high volume (n = 652, 40%), followed by high volume to high volume (n = 605, 37%), then low volume to low volume (n = 318, 20%), and the rare high volume to low volume (n = 50, 3%). Women retained in low-volume centers after biopsy were older, were less likely to have private insurance, and had more comorbidities. High-risk histology (aRR, 1.14; 95% confidence interval, 1.04–1.25) was positively associated with referral, while Medicaid insurance was negatively associated with referral (aRR, 0.64; 95% confidence interval, 0.42–0.96). Most women (74%, n = 1557) had surgery at high-volume centers. Lymphadenectomy was less likely at low-volume centers (aRR, 0.71; 95% confidence interval, 0.64–0.77). Similarly, for high-risk patients, the relationship between low-volume center surgery and subsequent chemotherapy was aRR, 0.71 (95% confidence interval, 0.48–1.02). Of 290 women who received chemotherapy, the referral patterns (surgery to chemotherapy) were: high volume—all (high volume to high volume), high volume–hybrid (high volume to low volume, or low volume to high volume), and high volume–none (low volume to low volume). In all, 36% (n = 104/290) received chemotherapy at a low-volume center, the majority (68%, n = 71/104) of whom were referred from high-volume centers after surgery. Crude, unadjusted mortality risk of chemotherapy recipients differed by referral pattern (surgery to chemotherapy): high volume—all patients (hazard ratio, 1.0; referent), followed by high volume–hybrid (hazard ratio, 1.33; 95% confidence interval, 0.93–1.91) then high volume–none patients (RR, 1.95; 95% confidence interval, 1.24–3.08).

**Conclusion** Most women with uterine cancer treated at high-volume centers arrive through referral, which is affected by age and type of insurance, in addition to histology. For high-risk women who require chemotherapy, survival may be related to the extent of treatment received at high-volume centers.

**Ultrasonographic diagnosis and longitudinal follow-up of recurrences after conservative surgery for borderline ovarian tumors.** D Franchi, S Boveri, D Radice, R Portuesi, V Zanagnolo, N Colombo, AC Testa. American Journal of Obstetrics and Gynecology in press. [https://www-clinicalkey-com.ezproxy.uky.edu/#!/content/journal/1-s2.0-S0002937816304586?scrollTo=%23hl0000729](https://www-clinicalkey-com.ezproxy.uky.edu/#!/content/journal/1-s2.0-S0002937816304586?scrollTo=%23hl0000729)
Background Borderline ovarian tumors are generally diagnosed in young women. Because of the young age of patients at first diagnosis and at recurrence, and given the good prognosis of borderline ovarian tumors, a conservative surgical approach in those women who wish to preserve their fertility is advised. In this scenario, transvaginal ultrasound examination plays a key role in the detection of borderline ovarian tumor recurrence, and in assessment of amount of normal functioning parenchyma remaining. To date, no data are available about the natural history of borderline ovarian tumor recurrence.

Objective The aim of the study was to determine growth rate of recurrent ovarian cysts by a scheduled follow-up by ultrasound examination, in women previously treated with fertility-sparing surgery due to borderline ovarian tumors.

Study Design In this prospective observational study, we collected data from 34 patients previously treated with fertility-sparing surgery due to borderline ovarian tumors, who had a suspicious recurrent lesion. The patients underwent transvaginal ultrasonographic examination every 3 months, until the clinical setting recommended proceeding with surgery. According to cyst size at study entry, they were categorized into 3 groups: ≤10 mm, 10-20 mm, and >20 mm.

Results Follow-up timing (P < .001), cyst size (P < .001), and micropapillary pattern (P < .001) were factors significantly affecting the cyst growth both in univariate and multivariate analysis. According to size category at first ultrasound, growth rate ranges from a minimum of 0.06 mm/mo for cysts <10 mm up to 1.92 mm/mo for cysts >20 mm. The final histology of all recurrent lesions confirmed the same histotype of primary borderline ovarian tumors.

Conclusion This article represents the first observational study that describes the trend in the growth rate of borderline ovarian tumor recurrence in relation to their size detected at the first ultrasound examination. The findings of this study seem to confirm, in selected patients, that a thorough ultrasonographic follow-up of borderline ovarian tumor recurrence has proven to be safe and feasible. The purpose of such management is to maximize the impact on fertility potential of these young women without worsening their prognosis.

Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. MG Dijkstra, M van Zummeren, L Rozendaal, FJ van Kemenade, TJ M Helmerhorst, PJF Snijders, CJLM Meijer, J Berkhof. BMJ 2016; 355 doi: http://dx.doi.org/10.1136/bmj.i4924

Objectives To provide an early risk assessment of extending screening intervals beyond five years for a human papillomavirus (HPV) based cervical screening programme in the Netherlands.

Design 14 year follow-up of a population based randomised cohort from the POBASCAM randomised trial.

Setting Organised cervical screening in the Netherlands, based on a programme of three screening rounds (each round done every five years).

Participants 43 339 women aged 29-61 years with a negative HPV and/or negative cytology test participating in the POBASCAM trial.

Interventions Women randomly assigned to HPV and cytology co-testing (intervention) or cytology testing only (control), and managed accordingly.

Main outcome measures Cumulative incidence of cervical cancer and cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+). Associations with age were expressed as incidence rate ratios. In HPV positive women, reductions in CIN3+ incidence after negative cytology, HPV type 16/18 genotyping, and/or repeat cytology were estimated.

Results The cumulative incidence of cervical cancer (0.09%) and CIN3+ (0.56%) among HPV negative women in the intervention group after three rounds of screening were similar to the cumulative among women with negative cytology in the control group after two rounds (0.09% and 0.69%, respectively). Cervical cancer and CIN3+ risk ratios were 0.97 (95% confidence interval 0.41 to 2.31, P=0.95) and 0.82 (0.62 to 1.09, P=0.17), respectively. CIN3+ incidence was 72.2% (95% confidence interval 61.6% to 79.9%, P<0.001) lower among HPV negative women aged at least 40 years than among younger women. No significant association between cervical cancer incidence and age could be demonstrated. CIN3+ incidence among HPV positive women with negative cytology, HPV 16/18 genotyping, and/or repeat cytology was 10.4 (95% confidence interval 5.9 to 18.4) times higher than among HPV negative women.

Conclusions Long term incidences of cervical cancer and CIN3+ were low among HPV negative women in this study cohort, and supports an extension of the cervical screening interval beyond five years for women aged 40 years and older. HPV positive women with subsequent negative cytology, HPV16/18 genotyping, and/or repeat cytology have at least a fivefold higher risk of CIN3+ than HPV negative women, indicating that HPV based programmes with long intervals (>five years) should be implemented with risk stratification.

August 2016


**REVIEW comparing cervical with oropharyngeal:** The incidence of oropharyngeal cancer (OPC) is significantly increasing in the United States. Given that these epidemiologic trends are driven by human papillomavirus (HPV), the potential impact of prophylactic HPV vaccines on the prevention of OPC is of interest. The primary evidence supporting the approval of current prophylactic HPV vaccines is from large phase 3 clinical trials focused on the prevention of genital disease (cervical and anal cancer, as well as genital warts). These trials reported vaccine efficacy rates of 89% to 98% for the prevention of both premalignant lesions and persistent genital infections. However, these trials were designed before the etiologic relationship between HPV and OPC was established. There are differences in the epidemiology of oral and genital HPV infection, such as differences in age and sex distributions, which suggest that the vaccine efficacy observed in genital cancers may not be directly translatable to the cancers of the oropharynx. Evaluation of vaccine efficacy is challenging in the oropharynx because no premalignant lesion analogous to cervical intraepithelial neoplasia in cervical cancer has yet been identified. To truly investigate the efficacy of these vaccines in the oropharynx, additional clinical trials with feasible endpoints are needed.

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**Background** The global economic crisis has been associated with increased unemployment and reduced public-sector expenditure on health care (PEH). We estimated the effects of changes in unemployment and PEH on cancer mortality, and identified how universal health coverage (UHC) affected these relationships.

**Methods** For this longitudinal analysis, we obtained data from the World Bank and WHO (1990–2010). We aggregated mortality data for breast cancer in women, prostate cancer in men, and colorectal cancers in men and women, which are associated with survival rates that exceed 50%, into a treatable cancer class. We likewise aggregated data for lung and pancreatic cancers, which have 5 year survival rates of less than 10%, into an untreatable cancer class. We used multivariable regression analysis, controlling for country-specific demographics and infrastructure, with time-lag analyses and robustness checks to investigate the relationship between unemployment, PEH, and cancer mortality, with and without UHC. We used trend analysis to project mortality rates, on the basis of trends before the sharp unemployment rise that occurred in many countries from 2008 to 2010, and compared them with observed rates.

**Results** Data were available for 75 countries, representing 2·106 billion people, for the unemployment analysis and for 79 countries, representing 2·156 billion people, for the PEH analysis. Unemployment rises were significantly associated with an increase in all-cancer mortality and all specific cancers except lung cancer in women. By contrast, untreatable cancer mortality was not significantly linked with changes in unemployment. Lag analyses showed significant associations remained 5 years after unemployment increases for the treatable cancer class. Rerunning analyses, while accounting for UHC status, removed the significant associations. All-cancer, treatable cancer, and specific cancer mortalities significantly decreased as PEH increased. Time-series analysis provided an estimate of more than 40 000 excess deaths due to a subset of treatable cancers from 2008 to 2010, on the basis of 2000–07 trends. Most of these deaths were in non-UHC countries.

**Interpretation** Unemployment increases are associated with rises in cancer mortality; UHC seems to protect against this effect. PEH increases are associated with reduced cancer mortality. Access to health care could underlie these associations. We estimate that the 2008–10 economic crisis was associated with about 260 000 excess cancer-related deaths in the Organisation for Economic Co-operation and Development alone.

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**Purpose** The clinicopathologic significance of mismatch repair (MMR) defects in endometrioid endometrial cancer (EEC) has not been definitively established. We undertook tumor typing to classify MMR defects to determine if MMR status is prognostic or predictive.

**Methods** Primary EECs from NRG/GOG0210 patients were assessed for microsatellite instability (MSI), MLH1 methylation, and MMR protein expression. Each tumor was assigned to one of four MMR classes: normal, epigenetic defect, probable mutation (MMR defect not attributable to MLH1 methylation), or MSI-low. The relationships between MMR classes and clinicopathologic variables were assessed using contingency table tests and Cox proportional hazard models.
**Results** A total of 1,024 tumors were assigned to MMR classes. Epigenetic and probable mutations in MMR were significantly associated with higher grade and more frequent lymphovascular space invasion. Epigenetic defects were more common in patients with higher International Federation of Gynecology and Obstetrics stage. Overall, there were no differences in outcomes. Progression-free survival was, however, worse for women whose tumors had epigenetic MMR defects compared with the MMR normal group (hazard ratio, 1.37; P < .05; 95% CI, 1.00 to 1.86). An exploratory analysis of interaction between MMR status and adjuvant therapy showed a trend toward improved progression-free survival for probable MMR mutation cases.

**Conclusion** MMR defects in EECs are associated with a number of well-established poor prognostic indicators. Women with tumors that had MMR defects were likely to have higher-grade cancers and more frequent lymphovascular space invasion. Surprisingly, outcomes in these patients were similar to patients with MMR normal tumors, suggesting that MMR defects may counteract the effects of negative prognostic factors. Altered immune surveillance of MMR-deficient tumors, and other host/tumor interactions, is likely to determine outcomes for patients with MMR-deficient tumors.

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Although epigenetic processes have been linked to aging and disease in other systems, it is not yet known whether they relate to reproductive aging. Recently, we developed a highly accurate epigenetic biomarker of age (known as the “epigenetic clock”), which is based on DNA methylation levels. Here we carry out an epigenetic clock analysis of blood, saliva, and buccal epithelium using data from four large studies: the Women's Health Initiative (n = 1,864); Invecchiare nel Chianti (n = 200); Parkinson's disease, Environment, and Genes (n = 256); and the United Kingdom Medical Research Council National Survey of Health and Development (n = 790). We find that increased epigenetic age acceleration in blood is significantly associated with earlier menopause (P = 0.00991), bilateral oophorectomy (P = 0.0018), and a longer time since menopause (P = 0.017). Conversely, epigenetic age acceleration in buccal epithelium and saliva do not relate to age at menopause; however, a higher epigenetic age in saliva is exhibited in women who undergo bilateral oophorectomy (P = 0.0079), while a lower epigenetic age in buccal epithelium was found for women who underwent menopausal hormone therapy (P = 0.00078). Using genetic data, we find evidence of coheritability between age at menopause and epigenetic age acceleration in blood. Using Mendelian randomization analysis, we find that two SNPs that are highly associated with age at menopause exhibit a significant association with epigenetic age acceleration. Overall, our Mendelian randomization approach and other lines of evidence suggest that menopause accelerates epigenetic aging of blood, but mechanistic studies will be needed to dissect cause-and-effect relationships further.

**Significance:** Within an evolutionary framework, aging and reproduction are intrinsically linked. Although both laboratory and epidemiological studies have observed associations between the timing of reproductive senescence and longevity, it is not yet known whether differences in the age of menopause are reflected in biomarkers of aging. Using our recently developed biomarker of aging, the “epigenetic clock,” we examined whether age at menopause is associated with epigenetic age of blood, saliva, and buccal epithelium. This is a definitive study that shows an association between age of menopause and biological aging (measured using the epigenetic clock). Our results also indicate menopause may accelerate the epigenetic aging process in blood and that age at menopause and epigenetic age acceleration share a common genetic signature.

**Question:** Will delaying menopause-influence aging be reflected in decreased cancer risk?
promising an “amazing” and “terrific” health-care plan to replace the ACA, Trump released on March 2, 2016, a two-page law he signed as governor requiring that all sixth-grade girls receive the HPV vaccine to reduce cervical cancer risk. After plan calls for reforms that would allow the sale of health insurance across state lines, tax deductions for individuals’ health “Healthcare Reform to Make America Great Again” plan. In addition to calling for a complete repeal of the ACA, Trump’s proposals for people whose employers offer insurance coverage to employees but not their families. Clinton’s running mate, US Senator and former Virginia Governor Tim Kaine, has been a strong advocate for cancer prevention policies, including a Medicare to negotiate better drug prices is not clear; both measures have been fiercely opposed by drug industry analysts like Sara Rosenbaum (George Washington University, Milken Institute, School of Public Health, Washington, DC, USA). “It is clear that we need a much more thoughtful market-wide solution to the problem, and for the USA to do what other nations do: step in and try to address these problems.” Tax deductions and tax-free Health Savings Accounts would not likely help the low-income patients who would lose Medicaid coverage under the Trump health-care plan, critics add. Trump claims that health care for illegal immigrants costs the US $11 billion a year (a figure for which no source is provided). His health-care plan calls for restricted granting of US visas to foreigners. By contrast, Clinton's plan would allow everybody, regardless of immigration status, to purchase insurance on the ACA exchanges. Trump's proposals for health-care policy have at times seemed contradictory. Despite his plan to repeal the ACA, for example, Trump has voiced support for the law’s prohibition on insurers denying coverage to patients because of pre-existing diseases. Trump has not explained how he would preserve this prohibition in the absence of the ACA's insurance “mandate”—the requirement that even healthy Americans have health insurance. Trump briefly expressed support for the mandate, too—but later said that he had intended to endorse protection for patients with pre-existing conditions, not the mandate. Whether either candidate could convince a Republican congress to allow patients to buy drugs overseas or to allow Medicare to negotiate better drug prices is not clear; both measures have been fiercely opposed by drug industry lobbyists and lawmakers alike. Kevin Brady, a Republican Congressman from Texas, said on July 19 that he would not support Trump’s plan to allow Medicare to negotiate drug prices. Other agencies, such as the US Veterans Administration

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and the Indian Health Service, are allowed to negotiate for better drug prices. But the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 forbids the US Department of Health and Human Services from negotiating prescription drug prices on behalf of Medicare beneficiaries. A Republican congress would probably enthusiastically support a repeal of the ACA, but repealing such a complex law and associated rules and regulations years into implementation would be no easy task and would risk public backlash. “The ACA changed the picture dramatically”, said Collins. “People who were uninsured, or who had serious health problems like cancer and became uninsured, faced the full cost of their care and went into debt; out-of-pocket spending was enormously high. Were the law to be repealed, you’d see people with cancer having to pay for their own care again, if they didn’t have coverage through their employers—and we know that people who are uninsured, get about half the care that they would otherwise get. Their cancers, in many cases, would very likely go untreated.”


Predatory publishers take notice: the US Federal Trade Commission (FTC) is coming for you. The FTC is taking a journal publisher, the OMICS Group, to court, alleging that the open-access operation and two of its subsidiaries misrepresent their editorial process and take advantage of academics seeking outlets for their work. The legal complaint, filed in the US District Court for the District of Nevada last week (August 25), marks the first time that the FTC has gone after so-called predatory publishers for questionable business practices, such as making up their own impact factors, charging authors exorbitant fees, and circumventing the peer-review process. Ioana Rusu, an attorney with the FTC, told Inside Higher Ed that a rising call from academics prompted the move. “There was definitely a sense that nobody had done anything about it,” she said. “Now we’re watching.” OMICS Group landed in hot water in 2013, when the US Department of Health and Human Services (HHS) told the publishing group to stop violating HHS trademarks by falsely claiming that OMICS papers were indexed by PubMed, PubMed Central, and other HHS databases—a claim reiterated in the FTC’s complaint. The conference arm of OMICS’s business is also mentioned in the FTC’s complaint, with the agency claiming that the publisher often promotes conferences in which attendees or speakers are listed without these people knowing about their supposed participation. “We take no sides between the traditional subscription model and the open-access model,” Rusu told Inside Higher Ed. “We believe both of them can be done in a fair, open, clear, and lawful way. What we have a problem with here is people who are trying to benefit from the open-access model to scam people.”

Objective: Some ovarian malignancies may originate in the fallopian tube. The feasibility of ultrasonographically visualizing the fallopian tube is presented.

Methods: In total, 549 normal women participated in the fallopian tube visualization trial, while ovarian visualization was studied in 43,521. Chi-square analysis, t-tests and multivariate analysis determined significance and interactions.

Results: Ovaries were observed in 82.7% while fallopian tubes were detected in 77.2% of women and 85.2% of the time when an ovary was detected. Age, BMI or parity was not significantly different when one or both fallopian tubes were visualized. Elevated BMI had slightly greater influence than age in limiting visualization of the fallopian tubes in multivariate analysis.

Conclusion: Fallopian tubes can often be identified sonographically. Ovarian visualization provides the strongest indicator favoring fallopian tube detection. Thus, ultrasonographic examinations for adnexal cancer could include evaluation of fallopian tubes even in women >60 years and in women with BMI ≥25.


BACKGROUND Whether higher grade cervical intraepithelial neoplasia (CIN grade 2 or greater [CIN ≥ 2]) that develops because of human papillomavirus (HPV) genotypes not included in vaccines may progress to cervical cancer is largely unknown. The objectives of this study were to document expression of the cyclin-dependent kinase inhibitor 2A (p16) tumor-suppressor protein p16INK4A as a biomarker of cervical carcinogenesis or of malignant potential and to evaluate whether its expression differs between lesions associated with vaccine and nonvaccine high-risk (HR) human papillomavirus (HPV) genotypes.

METHODS The study population consisted of 371 women who had not received HPV vaccines. Women were categorized into vaccine and nonvaccine HR-HPV genotypes and lesions associated with those types. Logistic regression analyses were used to determine the association between positive expression p16INK4A and the risk of being diagnosed with CIN 2 or CIN 3. Differences in the proportion of CIN ≥2 lesions that were positive for p16INK4A expression by vaccine-related or nonvaccine-related HR-HPV genotype were determined using the Pearson chi-square test.

RESULTS Specimens that were positive for p16INK4A expression were 5.3 and 16.6 times more likely to be diagnosed as CIN 2 and CIN 3 lesions, respectively, compared to CIN 1 lesions. CIN ≥ 2 lesions that were negative for the bivalent and 9-valent HR-HPV genotypes had similar rates of positive p16INK4A expression compared with lesions that were positive for those HR-HPV genotypes.

CONCLUSIONS Lesions that may develop because of HR-HPV genotypes not included in HPV vaccines are likely to have similar malignant potential, suggesting that well developed screening programs combined with nonvaccine-based approaches may be needed to manage the residual risk of developing cervical cancer in the post-HPV vaccination era.


As the promise and the pitfalls of precision medicine gain increasing attention, enthusiasm about the field has been heightened by a rapid reduction in the cost of high-throughput genomic sequencing and a dramatic increase in the identification of potential molecular targets for therapy. Biomarker tests for molecularly targeted therapies can help physicians to select the most effective therapy for a patient's condition and avoid treatments that could be ineffective or harmful. If precision medicine is to reach its potential, such biomarker tests will have to be developed in a timely fashion.

Some observers, however, have expressed concern that these rapid developments have caused genomic data to accumulate at a rate that exceeds our ability to adequately capture, fully analyze, and properly interpret them. The medical armamentarium available to physicians seeking to tailor therapies to their patients' conditions is expanding in parallel. Annual spending on molecularly targeted therapies for oncology in the United States now exceeds $10 billion, outpacing spending on conventional chemotherapies. In 2015 alone, the Food and Drug Administration approved 18 new agents for cancer, nearly all of which were based on the principles of precision medicine. The degree to which physicians will be able to apply genomic information in selecting therapy that improves clinical care remains to be seen and will probably vary over the near term.3,4 The processes of identifying and validating biomarker tests and of developing and evaluating targeted therapies are complex. Potentially useful tests have not been adopted into clinical practice rapidly, in
part because we lack common evidentiary standards for regulatory, clinical, coverage, and reimbursement decisions. Furthermore, clinical implementation will require the consistent collection and sharing of data on biomarker tests, treatments, and patient outcomes. The Institute of Medicine (IOM) has convened several expert committees over the past few years to consider a range of issues related to biomarkers, biomarker testing, genomics, and related disciplines. These efforts have highlighted the need for a systematic examination of all the challenges and opportunities associated with biomarker assays for molecularly targeted therapies. Most recently, the IOM assembled a Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularily Targeted Therapies (on which the authors served) to study and make recommendations about relevant regulatory, reimbursement, and clinical practice issues. The committee's report (nas.edu/biomarkers), released in March, provides 10 specific but wide-ranging recommendations based on the premise that properly validated and implemented biomarker tests and targeted therapies hold considerable promise for enhancing the quality of patient care and improving meaningful clinical outcomes (see IOM Committee Recommendations for Advancing Appropriate Use of Biomarker Tests for Molecularily Targeted Therapies). First and foremost, the committee calls for the development of common standards for assessing the utility of biomarker tests in the selection of targeted therapies and improvement of patient outcomes. Such standards would inform regulatory oversight of test development and approval, appropriate clinical adoption and utilization, and decisions about coverage and reimbursement. Interoperability and integration of electronic health records and laboratory information systems, ideally by means of a national database for health care providers and patients, would enhance the sustainable implementation and continuous evaluation of such tests. The committee further recommends that equitable access to biomarker tests and targeted therapies be ensured through patient and provider education, simplified and informative labeling, and supportive reimbursement policies. The committee's recommendations are meant to guide both the development of evidence supporting initial clinical application of biomarker tests and the ongoing assessment of their benefit. Given that the apparent value or benefit of biomarkers for a molecularily targeted therapy may vary considerably, a primary goal of the committee's recommendations is to increase patients' access to appropriate, accurate, reliable tests that can direct personalized or precision therapy. The committee pursued its work against the backdrop of President Barack Obama's Precision Medicine Initiative, which aims to empower clinicians, patients, and investigators to work together toward more personalized care and improved clinical outcomes and includes the development of a large patient cohort from which both clinical and “omics” data would be collected. Relevant congressional actions include the 21st Century Cures bill in the House of Representatives and companion bills in the Senate. In addition, President Obama has asked Vice President Joe Biden to take charge of a new Cancer Moonshot Initiative aimed at developing a large, interoperable, and fully integrated database to accelerate cancer discovery and innovation and at improving the delivery of such advances to patients and health care providers. If it is developed and maintained in a rigorous, evidence-based fashion with well-designed and well-executed studies, precision medicine could rapidly advance the care of patients with cancer and other diseases by tailoring treatment to individual patients' conditions and improving clinical outcomes and quality of life, while reducing costs by averting the use of ineffective or harmful therapies. However, precision medicine comes with the methodologic challenges associated with small target populations, as well as the reimbursement challenges associated with an increasingly value-sensitive health care delivery environment. Moreover, there is potential for the unintended consequence of intensifying disparities in access to advanced health care services, including biomarker testing and molecularily targeted therapies. Before such biomarker tests become part of standard care, it is essential to establish that such tests are accurate and reliable (have analytic validity), are associated with the disease and outcome of interest (clinical validity), and actually lead to improved patient outcomes as compared with standard treatment (clinical utility). This process starts with the establishment of the reliability, accuracy, and precision of the test based on rigorous laboratory studies. Molecularly targeted agents should be administered only if a specific biomarker that predicts the effectiveness of the therapy is known to be present on the basis of a validated assay. When the effectiveness and safety of a therapy depends on the status of a biomarker, the test becomes as important as the treatment for optimal patient care. There is also a need for consensus on the evidence required to adequately establish clinical utility for initial use; the assessment of utility may change over time, as evidence accumulates and new tests and treatments are developed. The line between clinical research and clinical care is likely to be blurred in the era of precision medicine. We believe it will be critical for health systems and individual providers to share in the responsibility for data capture and integration until there is sufficient evidence to determine whether a given test has actual clinical utility. Payers will also have to share in the responsibility for coverage and reimbursement as the evidence is refined. Finally, everyone involved will have to work to ensure that patients have fair and equitable access to promising as well as established biomarker tests for molecularly targeted therapies. A national initiative involving not only clinicians and laboratory scientists but also experts in informatics could continuously capture, catalogue, and annotate data on biomarkers and targeted therapies and make them available to regulators, providers, payers, and patients who want to take a more active role in shared decision making. We believe these steps will enable precision medicine to fulfill its potential for improving patient care and clinical outcomes.

**IOM COMMITTEE RECOMMENDATIONS FOR ADVANCING APPROPRIATE USE OF BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES.**

1. The secretary of health and human services (HHS) should facilitate the development of common evidentiary standards for clinical utility that are applied in making initial and ongoing coordinated regulatory, coverage, and reimbursement decisions regarding biomarker tests for molecularly targeted therapies. One mechanism for development of these evidentiary standards could be convening one or more independent, public–private, multistakeholder bodies.
2. The secretary of HHS should facilitate the development of a new integrated federal review process involving the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS).
3. The FDA should develop a patient- and provider-friendly standardized label for in vitro diagnostic and laboratory-developed biomarker tests to facilitate transparency of test performance characteristics and the level of evidence for the intended use or uses of the test.
4. The secretary of HHS should establish and enforce up-to-date laboratory accreditation standards for biomarker tests for molecularly targeted therapies, either through CMS’s Clinical Laboratory Improvement Amendments or in collaboration with an existing, up-to-date accreditation organization.
5. When existing evidence of clinical utility is sufficient for initial use of a biomarker test for a molecularly targeted therapy, CMS and other payers should develop reimbursement models that support the ongoing collection of data within a rapid learning system.
6. Electronic health record (EHR) and laboratory information system vendors and relevant software developers should enable the capture and linkage of biomarker tests, molecularly targeted therapies, and longitudinal clinical patient data in the EHR to facilitate data transfer into one or more national databases.
7. The secretary of HHS should charge the FDA and the National Institutes of Health with convening a task force to develop a sustainable national repository of biomarker tests, molecularly targeted therapies, and longitudinal clinical patient data to facilitate rapid learning approaches.
8. Agencies that fund the development or evaluation of biomarkers should include funding for identifying and overcoming barriers to the promotion of equity, access, and public understanding of precision medicine.
9. Professional organizations and accrediting entities should develop, and health care institutions and providers should implement, standards for specimen requirements, handling, and documentation through an interdisciplinary effort.
10. Guideline-developing organizations should expand interdisciplinary collaborations to develop integrated guidelines on the appropriate use of biomarker tests for molecularly targeted therapies.


Objective We describe current evidence for staging low malignant potential ovarian tumors and their conformity to current consensus guidelines and practice from an international perspective.

Data Sources A search of MEDLINE, EMBASE, and SCOPUS databases was conducted for articles published between January 1990 and April 2015.

Study Eligibility Criteria Studies on low malignant potential ovarian tumors that evaluated the prognostic value of disease stage, staging vs no staging, complete vs incomplete staging, or discrete components of staging were eligible. Studies that described only crude survival rates were excluded.

Study Appraisal and Synthesis Methods Eligible studies were categorized according to their outcome (disease stage, staging procedure, or discrete staging elements). Data were abstracted using a standard form. Inconsistencies on data abstraction were resolved by consensus among the authors. Risk of bias was assessed using the Newcastle-Ottawa Scale.

Results Of 1116 studies, 702 were excluded for irrelevance and 364 for not meeting inclusion criteria. Nine studies were excluded for describing crude survival rates without a comparative conclusion. We found that studies supporting the value of defining disease stage or staging procedures (mostly conducted in northern Europe) included more patients than studies that did not find disease stage or staging useful (predominantly from North America, 4072 vs 3951). Disease stage correlated with survival in 13 of 25 studies, whereas none of the studies that evaluated the value of staging found it beneficial (9 studies, 1979 patients). Studies that evaluated isolated components of staging found no benefit to these procedures. Regional guidelines and consensus reviews drew conclusions based on a limited number of studies that generally originated from the same region.

Conclusions Although the correlation of stage with survival was mixed, performing staging procedures for low malignant potential ovarian tumors is not supported by the best available evidence. Guidelines in support of staging based their recommendations on a few regional studies and conflict with better-quality data that do not support staging procedures. An international consensus statement is needed to standardize the surgical management of low malignant potential ovarian tumors.


Background Risk of relapse or progression remains high in the treatment of most patients with epithelial ovarian cancer,
Methods We analysed miRNA expression profiles in three cohorts of samples collected at diagnosis. We used 179 samples from a Multicenter Italian Trial in Ovarian cancer trial (cohort OC179) to develop the model and 263 samples from two cancer centres (cohort OC263) and 452 samples from The Cancer Genome Atlas epithelial ovarian cancer series (cohort OC452) to validate the model. The primary clinical endpoint was progression-free survival, and we adapted a semi-supervised prediction method to the miRNA expression profile of OC179 to identify miRNAs that predict risk of progression. We assessed the independent prognostic role of the model using multivariable analysis with a Cox regression model.

Findings We identified 35 miRNAs that predicted risk of progression or relapse and used them to create a prognostic model, the 35-miRNA-based predictor of Risk of Ovarian Cancer Relapse or progression (MiROvaR). MiROvaR was able to classify patients in OC179 into a high-risk group (89 patients; median progression-free survival 18 months [95% CI 15–22]) and a low-risk group (90 patients; median progression-free survival 38 months [24–not estimable]; hazard ratio [HR] 1.85 [1.29–2.64], p=0.0082). MiROvaR was a significant predictor of progression in the two validation sets (OC263 HR 3.16, 95% CI 2.33–4.29, p<0.0001; OC452 HR 1.39, 95% CI 1.11–1.74, p=0.0047) and maintained its independent prognostic effect when adjusted for relevant clinical covariates using multivariable analyses (OC179: adjusted HR 1.48, 95% CI 1.03–2.13, p=0.036; OC263: adjusted HR 3.09 [2.24–4.28], p<0.0001; and OC452: HR 1.41 [1.11–1.79], p=0.0047).

Interpretation MiROvaR is a potential predictor of epithelial ovarian cancer progression and has prognostic value independent of relevant clinical covariates. MiROvaR warrants further investigation for the development of a clinical-grade prognostic assay.

Adjuvant Pelvic Radiation Therapy±Vaginal Brachytherapy in Patients With High-risk Stage I or Stage II Uterine Papillary Serous, Clear Cell, and High-grade Endometrioid Carcinoma.

Nagar, H; Yan, W; Parashar, B; Nori, D; Chao, K.S.C, Christos, P; Gupta, D; Holcomb, K; Caputo, T; Wernicke, AG. American Journal of Clinical Oncology Issue: Volume 39(4), August 2016, p 335–339
http://ovidsp.tx.ovid.com.ezproxy.uky.edu/sp-3.21.0a/ovidweb.cgi?&S=LPBCFPRLBIDDEFKNKNCIIHHDCDDJBA00&Link+Set=S.sh.22.23.26%7c18%7csl_10

Purpose: Radiation therapy (RT) for stages I-II uterine papillary serous carcinoma (UPSC), clear cell (CC), and high-grade endometrioid (HGE) carcinoma present a treatment challenge. Regimens include external beam radiotherapy (EBRT) with or without brachytherapy. We examine the use of these radiation modalities in these endometrial cancers (EC) with respect to cause-specific survival (CSS).

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for patients with AJCC stages I-II UPSC, CC, or HGE cancer treated with hysterectomy and RT between 1998 and 2008. Patients who did not receive adjuvant RT or received brachytherapy alone were excluded. CSS was evaluated by the Kaplan-Meier survival analysis and the log-rank test was used to compare CSS. Multivariate analysis was performed using the Cox proportional hazards regression model. Adjusted hazard ratios (HR) were calculated for risk of EC death.

Results: There were 1653 patients included in this analysis. The overall 100-month CSS for the entire cohort was 81.0%. The 100-month CSS was 85.3% for EBRT alone and 86.5% for EBRT+brachytherapy (P=0.72). Stage IC/IIA/IIIB patients had a greater risk of EC death compared with stage IA/IB patients (adjusted HR=2.39; P<0.0001). Patients with UPSC and CC had a slightly higher risk of EC death compared with HGE (adjusted HR=1.01 [P=0.97] and 1.42 [P=0.02], respectively). On subset analysis, there was no difference in CSS with the addition of brachytherapy for UPSC (P=0.37), CC (P=0.27), or HGE cancer patients (P=0.42). Patients treated with brachytherapy in addition to EBRT did not demonstrate a reduced adjusted risk of EC death compared with EBRT alone (P=0.38).

Conclusions: The addition of brachytherapy to adjuvant EBRT in stages I-II UPSC, CC, and HGE cancer did not demonstrate superior CSS. Thus, patients may not benefit from the addition of brachytherapy to EBRT.

http://ovidsp.tx.ovid.com.ezproxy.uky.edu/sp-3.21.0a/ovidweb.cgi?&S=LPBCFPFLBIDDEFKNKNCIIHHDCDDJBA00&Link+Set=S.sh.22.23.26%7c18%7csl_10

Recently in the American Journal of Clinical Oncology (Am J Clin Oncol. 2016;39:107), Dr Kimberly Perez nicely emphasized an important pitfall of next-generation sequencing (NGS) for the purpose of identifying actionable somatic mutations. She noted that in the experience at Rhode Island Hospital 50 of 68 cancer patients (73.5%) had somatic mutations known to be associated with familial cancer syndromes. She also reminded us that for most of these mutations it is unknown, in the setting of a family history not suggestive of the syndrome associated with the corresponding germline mutation, whether such testing should be pursued.

I would emphasize that her concerns are further compounded once a germline mutation is identified. As an example, I recently was asked to see a patient who was found to harbor a germline BRIP mutation (BRIP1 c.1741C>7 [p.Arg581*]) by NGS. Her family history was not suggestive of a significant pretest likelihood of carrying a germline mutation in this case.
particular gene. Nevertheless, the report from Myriad Genetics Inc.2 stated that the patient had “high cancer risk” due to this mutation (for breast cancer as high as 12-fold higher compared with the general population) and the National Comprehensive Cancer Network Guidelines suggests “consider chemoprevention options” in some patients with the BRIP germline mutation due to the associated breast cancer risk.3 However, as in the case of the uncertainty of somatic mutations and the likelihood of a corresponding germline mutation, it remains unclear as to whether an incidentally discovered germline mutation implies as high a penetrance as one discovered based on testing for that specific hereditary cancer susceptibility. Also, the 50% reduction in the risk of developing breast cancer with chemoprevention (eg, with tamoxifen, raloxifene) was seen for patients with a 1.66-fold increased risk calculated using the Gail Model.4 Even if it were possible to conflate a 12-fold increased lifetime risk with a 5-year risk of 1.66-fold risk or greater than the general population, the benefit of chemoprevention should not be assumed to true for any patient with a 1.66-fold or greater increased risk, but perhaps only those where the risk is predicted based on the Gail Model criteria for generating that score.3 Physicians and their patients need to be aware of not only the pitfalls highlighted by Dr Perez in screening tumors using NGS but also those uncertainties likely to occur when one pursues NGS testing of patients for germline mutations.

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**Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline.**

AA Wright, K Bohlke, DK. Armstrong, MA Bookman, WA Cliby, RL Coleman, DS Dizon, JJ Kash, LA Meyer, K N Moore, AB Olawaiye, J Oldham, R Salani, D Sparacio, WP Tew, I Vergote, MI Edelson. Published online before print August 8, 2016, doi: 10.1200/JCO.2016.68.6907 [http://jco.ascopubs.org/content/early/2016/08/04/JCO.2016.68.6907.full](http://jco.ascopubs.org/content/early/2016/08/04/JCO.2016.68.6907.full)

**Purpose** To provide guidance to clinicians regarding the use of neoadjuvant chemotherapy and interval cytoreduction among women with stage IIIC or IV epithelial ovarian cancer.

**Methods** The Society of Gynecologic Oncology and the American Society of Clinical Oncology convened an Expert Panel and conducted a systematic review of the literature.

**Results** Four phase III clinical trials form the primary evidence base for the recommendations. The published studies suggest that for selected women with stage IIIC or IV epithelial ovarian cancer, neoadjuvant chemotherapy and interval cytoreduction are noninferior to primary cytoreductive chemotherapy with respect to overall progression-free survival and are associated with less perioperative morbidity and mortality.

**Recommendations** All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy. The primary clinical evaluation should include a CT of the abdomen and pelvis, and chest imaging (CT preferred). Women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to <1 cm of residual disease (ideally to no visible disease) should receive neoadjuvant chemotherapy. Women who are fit for primary cytoreductive surgery, and with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery. However, primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to <1 cm (ideally to no visible disease) with acceptable morbidity. Before neoadjuvant chemotherapy is delivered, all patients should have confirmation of an invasive ovarian, fallopian tube, or peritoneal cancer. Additional information is available at [www.asco.org/NACT-ovarian-guideline](http://www.asco.org/NACT-ovarian-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki).

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**CRISPR: No Cutting Required---Combining a modified Cas9 enzyme with an unrelated one derived from the immune system of the sea lamprey, researchers demonstrate yet another way to edit a single DNA nucleotide.**

A Azvolinsky | August 4, 2016 The Scientist [http://www.the-scientist.com/?articles.view/articleNo/46724/title/CRISPR--No-Cutting-Required/&utm_campaign=NEWSLETTER_TS_The-Scientist-Daily_2016&utm_source=hs_email&utm_medium=email&utm_content=32546598&_hsenc=p2ANqtz-8DrMoJ0Xrmmnpyw7Xg9V-RVkjc0MnZvd8xRm9-Vp-1qyf_jSLpbwvXW5hDTTzvo8weJHrrwbIE7MjDAg5DpdpOBwa&_hsml=32546598](http://www.the-scientist.com/?articles.view/articleNo/46724/title/CRISPR--No-Cutting-Required/&utm_campaign=NEWSLETTER_TS_The-Scientist-Daily_2016&utm_source=hs_email&utm_medium=email&utm_content=32546598&_hsenc=p2ANqtz-8DrMoJ0Xrmmnpyw7Xg9V-RVkjc0MnZvd8xRm9-Vp-1qyf_jSLpbwvXW5hDTTzvo8weJHrrwbIE7MjDAg5DpdpOBwa&_hsml=32546598)

Taking advantage of a deaminase enzyme that introduces a single nucleotide change to DNA, researchers have created a modified CRISPR/Cas9 tool that avoids the generation of a deleterious double-stranded break, minimizes the potential for the introduction of collateral mutations, and does not require the addition of a DNA template. The new method, described today (August 4) in Science, is the second reporting of such a precise gene-editing tool. “These deaminases solve the biggest problems with most previous genome-editing methods, including TALENs, zinc finger nucleases, and Cas9, which is that the desired edits are in competition with random insertions and deletions via non-homologous end-joining (NHEJ),” wrote Harvard University’s George Church whose lab has also developed a deaminase-based base-editing tool. The newly described system “also reduces the toxicity caused by double stranded breaks,” he added. “It is always encouraging and helpful for the field when another lab replicates a major finding,” said David Liu, a professor of chemical biology at Harvard University whose lab recently described a similar technique using a different deaminase enzyme. “The authors here were also able to demonstrate that this gene editing strategy works in cells.” With the CRISPR/Cas9 system, researchers edit a DNA sequence by introducing Cas9 into a cell, which creates a double-stranded break, and a DNA template that the cell uses to repair that break. This editing process relies on the cell’s
Human papillomavirus (HPV) causes almost all cervical cancers and most other anogenital cancers and warts in both men and women. Worldwide prevalence is 11.7% in women, causing 4.5% of new cancers in women each year. Despite an effective vaccine being licensed in 2006, only last week was it approved for girls in China and endorsed for boys in the USA. In China, this unacceptable drug approval lag is not limited to HPV vaccination—the problem is deeply rooted in the Chinese drug approval system. Trial registration is lengthy, with no prioritisation mechanism in place. Additionally, similar to some other countries, no drug can be licensed in China until clinical trials have been done in the country. Trials were done between 2002 and 2005 in other Asian countries but were not accepted by the Chinese Government, with a Chinese homologous recombination machinery but other repair mechanisms, including NHEJ, compete to execute the repair, often resulting in unwanted and imprecise insertions and/or deletions. “During double-stranded break repair, many things are going on at once and sometimes nucleotides are deleted and inserted or mutated in a way that is out of our control,” study coauthor Akihiko Kondo, of Kobe University in Japan, told The Scientist. To create a more precise gene-editing tool, Kondo and colleagues fused either a nuclease-dead version of Cas9 that cannot cleave double-stranded DNA or a sea lamprey-derived “nickase” Cas9 that creates a nick (a single-stranded break) with the activation-induced cytidine deaminase (AID). The AID enzyme normally creates mutations in immunoglobulin and antibody genes to generate immune system diversity. AID works on single-stranded DNA, substituting a cytosine (C) to a uracil (U) base, which is then converted into a thymine (T) in the next round of DNA replication. Testing the ability of the new hybrid complex to modify a selectable marker in budding yeast, which lack an endogenous AID-like system, the team found that when the protein complex was targeted to the CAN1 gene by guide RNA, the frequency of CAN1 mutations increased 1,000-fold compared to a non-targeted selectable marker. Using whole-genome sequencing, the researchers showed few off-target mutations with only a slight increase in the background mutation rate. “The mutation rate [in the presence of AID] is acceptable, less than 10-fold higher compared to the natural background mutation rate,” said study coauthor Keiji Nishida, a postdoctoral fellow in the Kondo lab. The researchers also demonstrated the ability to make modifications to two genes simultaneously by expressing two different guide RNAs along with the Cas9-deaminase complex. The complex with the nickase Cas9, which creates a nick in the opposite strand to where the nucleotide substitution occurs, was slightly more efficient compared to the one with the nuclease-dead Cas9 complex, the researchers showed. Because nucleotide excision repair can repair the nucleotide substitution created by AID, “if a nick is created in the complimentary strand, there is no longer a reference to correct the substitution mutation,” making the wanted nucleotide substitution process more efficient, Nishida explained. Further, the researchers linked an additional enzyme—a uracil-DNA glycosylase inhibitor—to the Cas9-deaminase complex, increasing the efficiency of the complex in creating cytosine-to-thymine substitutions and minimizing the creation of inadvertent deletion mutations in mammalian cell lines. The modified gene-editing complex also worked well in mammalian cell lines and resulted in relatively few off-target mutations. In yeast, expression of either version of the DNA-editing complex resulted in better growth compared to cells that expressed the standard CRISPR/Cas9 system, suggesting that the new tool is also less toxic. The so-called Target-AID complex had high specificity, modifying a cytosine within a three to five base pair window within the target gene, the team reported. “We were surprised that the mutation window was so very narrow,” said Nishida. By comparison, Liu and his colleagues reported variants of their base-editing tool—using a deaminase derived from rats—with windows ranging between three and six nucleotides. “To be maximally useful, the base-editing window needs to be neither too wide nor too narrow so it is helpful that both of these approaches offer researchers more choices, increasing the chance that they can solve their base-editing need,” Liu told The Scientist. For Church, further developing this tool for clinical applications will require extensive examination of potential off-target effects. Another open question, he noted, is how to target a specific cytosine without hitting adjacent cytosines in the target sequence. According to Kondo, the team is now working to link Cas9 with other enzymes to create a full range DNA-editing kit capable of creating any of the four nucleotide substitution combinations.


Human papillomavirus (HPV) causes almost all cervical cancers and most other anogenital cancers and warts in both men and women. Worldwide prevalence is 11.7% in women, causing 4.5% of new cancers in women each year. Despite an effective vaccine being licensed in 2006, only last week was it approved for girls in China and endorsed for boys in the USA. In China, this unacceptable drug approval lag is not limited to HPV vaccination—the problem is deeply rooted in the Chinese drug approval system. Trial registration is lengthy, with no prioritisation mechanism in place. Additionally, similar to some other countries, no drug can be licensed in China until clinical trials have been done in the country. Trials were done between 2002 and 2005 in other Asian countries but were not accepted by the Chinese Government, with a Chinese trial started in 2008 finally leading to approval this year. Travel agencies even offer package deals from the mainland to Hong Kong for HPV vaccinations to circumvent the problem. Improvement efforts are underway, such as a so-called four-colour light strategy for prioritisation and hiring of more staff to wade through the application backlog. In the USA, despite approval for girls in 2006 and boys in 2011, uptake has been shockingly low. In 2014, just 37% of girls received the three-dose course compared with 13% of boys. Misconceptions have driven the low uptake, including the belief that vaccination is only needed for sexually active individuals or that vaccination of preteens will cause them to become sexually active. These misunderstandings have weakened political will to mandate the vaccine. Often, parents have not heard about the vaccine or believe that it is not needed. Politicians, health-care professionals, and parents all need to understand the importance of the vaccine. To deny girls and boys the full protection of the vaccine can no longer be tolerated. The HPV vaccine has proven efficacy. But a decade on, its uptake has been poor, with a worldwide coverage of only 1.4% of women. Vaccines are one of the strongest levers to improve public health; their study, licensing, and implementation require more urgency than China and the USA have so far displayed.
Massively Parallel Sequencing-Based Clonality Analysis of Synchronous Endometrioid Endometrial and Ovarian Carcinomas


Synchronous early-stage endometrial endometrial carcinomas (EECs) and endometrioid ovarian carcinomas (EOCs) are associated with a favorable prognosis and have been suggested to represent independent primary tumors rather than metastatic disease. We subjected sporadic synchronous EECs/EOCs from five patients to whole-exome massively parallel sequencing, which revealed that the EEC and EOC of each case displayed strikingly similar repertoires of somatic mutations and gene copy number alterations. Despite the presence of mutations restricted to the EEC or EOC in each case, we observed that the mutational processes that shaped their respective genomes were consistent. High-depth targeted massively parallel sequencing of sporadic synchronous EECs/EOCs from 17 additional patients confirmed that these lesions are clonally related. In an additional Lynch Syndrome case, however, the EEC and EOC were found to constitute independent cancers lacking somatic mutations in common. Taken together, sporadic synchronous EECs/EOCs are clonally related and likely constitute dissemination from one site to the other.

Synchronous Endometrial and Ovarian Carcinomas: Evidence of Clonality


Many women with ovarian endometrioid carcinoma present with concurrent endometrial carcinoma. Organ-confined and low-grade synchronous endometrial and ovarian tumors (SEOs) clinically behave as independent primary tumors rather than a single advanced-stage carcinoma. We used 18 SEOs to investigate the ancestral relationship between the endometrial and ovarian components. Based on both targeted and exome sequencing, 17 of 18 patient cases of simultaneous cancer of the endometrium and ovary from our series showed evidence of a clonal relationship, i.e., primary tumor and metastasis. Eleven patient cases fulfilled clinicopathological criteria that would lead to classification as independent endometrial and ovarian primary carcinomas, including being of FIGO stage T1a/1A, with organ-restricted growth and without surface involvement; 10 of 11 of these cases showed evidence of clonality. Our observations suggest that the disseminating cells amongst SEOs are restricted to physically accessible and microenvironment-compatible sites yet remain indolent, without the capacity for further dissemination.

Interactions with industry under the Sunshine Act: an example from gynecologic oncology


The Problem Clinicians may be unaware that industry payments to physicians are now publicly searchable under the Physician Payments Sunshine Act. Furthermore, the extent of industry’s financial involvement in subspecialty practice has not been previously accessible. As an example, 6948 direct, research-unrelated payments totaling $1,957,004 were made to 765 gynecologic oncologists in 2014, the first full year of data available. A total of 153 companies reported at least 1 payment; however, the 10 manufacturers reporting the highest total payment amount accounted for 82% of all payments to physicians. In all, 48 gynecologic oncologists received >$10,000 from manufacturers, accounting for $1,202,228, or 61%, of total payments.

A Solution Obstetrician-gynecologists, including gynecologic oncologists, should be aware of their publicly reported payments from industry and ensure reports’ accuracy. Professional organizations, including the Society of Gynecologic Oncology (SGO), should strongly consider proactively developing guidelines regarding interactions with industry for their general memberships.

Sunshine Act: Shedding Light on Inaccurate Disclosures at a Gynecologic Annual Meeting

RSS Download PDF.
Background Physicians and hospital systems often have relationships with biomedical manufacturers to develop new ideas, products, and further education. Because this relationship can influence medical research and practice, reporting disclosures is necessary to reveal any potential bias and inform consumers. The Sunshine Act was created to develop a new reporting system of these financial relationships called the Open Payments database. Currently, all disclosures submitted with research to scientific meetings are at the discretion of the physician. We hypothesized that financial relationships between authors and medical industry are underreported.

Objectives We aimed to describe concordance between physicians’ financial disclosures listed in the abstract book from the 41st Annual Society of Gynecologic Surgeons’ (SGS) Scientific Meeting to physician payments reported to the Center for Medicaid and Medicare Services’ (CMS) Open Payments database for the same year.

Study Design Authors and scientific committee members responsible for the content of the 41st SGS Scientific Meeting were identified from the published abstract book; each abstract listed disclosures for each author. Abstract disclosures were compared to transactions recorded on the CMS Open Payments database for concordance. Two authors reviewed each non-disclosed CMS listing to determine relatedness between the company listed on CMS and abstract content.

Results Abstracts and disclosures of 335 physicians meeting inclusion criteria were reviewed. 209/335 (62%) physicians had transactions reported in CMS that totaled $1.99 million. 24/335 (7%) physicians listed companies with their abstracts; 5 of those 24 physicians were concordant with CMS. The total amount of all non-disclosed transactions was $1.3 million. Transactions reported in CMS associated with a single physician ranged from $11,72 to $405,903.36. Of the 209 physicians with CMS transactions that were not disclosed, the majority (68%) had at least one company listed in CMS that was determined after review to be related to the subject of their abstract.

Conclusion Voluntary disclosure of financial relationships was poor, and the majority of unlisted disclosures in the abstract book were companies related to the scientific content of the abstract. Better transparency is needed by physicians responsible for the content presented at gynecologic scientific meetings.


Background The global economic crisis has been associated with increased unemployment and reduced public-sector expenditure on health care (PEH). We estimated the effects of changes in unemployment and PEH on cancer mortality, and identified how universal health coverage (UHC) affected these relationships.

Methods For this longitudinal analysis, we obtained data from the World Bank and WHO (1990–2010). We aggregated mortality data for breast cancer in women, prostate cancer in men, and colorectal cancers in men and women, which are associated with survival rates that exceed 50%, into a treatable cancer class. We likewise aggregated data for lung and pancreatic cancers, which have 5 year survival rates of less than 10%, into an untreatable cancer class. We used multivariable regression analysis, controlling for country-specific demographics and infrastructure, with time-lag analyses and robustness checks to investigate the relationship between unemployment, PEH, and cancer mortality, with and without UHC. We used trend analysis to project mortality rates, on the basis of trends before the sharp unemployment rise that occurred in many countries from 2008 to 2010, and compared them with observed rates.

Results Data were available for 75 countries, representing 2.106 billion people, for the unemployment analysis and for 79 countries, representing 2.156 billion people, for the PEH analysis. Unemployment rises were significantly associated with an increase in all-cancer mortality and all specific cancers except lung cancer in women. By contrast, untreatable cancer mortality was not significantly linked with changes in unemployment. Lag analyses showed significant associations remained 5 years after unemployment increases for the treatable cancer class. Retraining analyses, while accounting for UHC status, removed the significant associations. All-cancer, treatable cancer, and specific cancer mortalities significantly decreased as PEH increased. Time-series analysis provided an estimate of more than 40,000 excess deaths due to a subset of treatable cancers from 2008 to 2010, on the basis of 2000–07 trends. Most of these deaths were in non-UHC countries.

Interpretation Unemployment increases are associated with rises in cancer mortality; UHC seems to protect against this effect. PEH increases are associated with reduced cancer mortality. Access to health care could underlie these associations. We estimate that the 2008–10 economic crisis was associated with about 260,000 excess cancer-related deaths in the Organisation for Economic Co-operation and Development alone.


One of the great myths peddled about cancer control is that it is intrinsically affordable. Nothing could be further from the truth. Preventing and treating cancer is the pinnacle of the health system’s mountain. It is the most demanding disease domain to address in health systems planning, as well as being highly sensitive to all the socio-cultural determinants of health. Those of us ‘inside’ the cancer tent take for granted these interdependencies, but to the ‘outside’, including most policy makers, cancer is a ‘black box’. This is a huge challenge to rational economic and fiscal policy-making. As the Institute of Medicine noted in its Delivering Affordable Cancer Care in the 21st Century report, “cancer is such a prevalent...
set of conditions and so costly, it magnifies what we know to be true about the totality of health care systems. It exposes all of its strengths and weakness." There are some eye-watering numbers around economic productivity losses due to cancer, particularly premature mortality and morbidity. Lung cancer costs Europe more than €10 billion every year in premature mortality, far outstripping the costs of direct cancer care of around €4.5 billion. And we know from the Lancet Oncology Commission on Global Cancer Surgery that a failure to deliver more surgical workforce, the backbone of cancer care, will cost low-income and emerging powers $7 trillion of cumulative GDP losses by 2030. The Global Taskforce on Radiotherapy also estimates similar losses. The point is not the huge figures, it’s that failure to invest in systems for cancer care is going to seriously impact development. Yet we are faced with a range of serious paradoxes. The first is the cold hard fact that many countries are failing miserably to invest in basic healthcare. Affordable and equitable cancer care cannot be built on sand, and this is just the situation facing many countries now. It’s all very well to sign up to Universal Health Coverage, the Sustainable Development Goals and National Cancer Control Plans, but in lowincome and emerging powers only a handful of countries have a total health expenditure above the threshold needed to build a cancer system (about 6% of GDP, and more than $100 per capita). The economies of Asia typify the problems affecting many countries: low domestic healthcare spending that is increasingly being backstopped by private health expenditure (Lancet 2011;377:863–872). In some Asian countries, such as Laos, Philippines and Cambodia, the private sector now makes up more than two-thirds of total health expenditure. Should this matter though? The short answer is yes it does. Only countries with dominant public sector financing, such as Thailand, can deliver equitable and sustainable economic policies to build cancer care. The sad fact is that the mantra from the World Bank and most of the overseas aid donors is that public fiscal policy in cancer is not that important, and gaps can be filled by business, contrary to the evidence from studies such as Global Health 2035 (Lancet 2013, 382:1898–1955). Economic sustainability in cancer control is also in serious doubt in many places. For example, take a stable African country like Uganda. As it stands, around half of the Sustainable Development Goal indicators are currently underperforming (World Bank Group. Country Diagnostics Jan. 2015). The other equally pressing issue is how to protect individuals and families from catastrophic health expenditure. Here too the picture is none too rosy. The Asian costs in oncology study (ACTION) looked at the economic impact of cancer on 9513 patients diagnosed with cancer between March 2012 and Sept 2013, who were recruited from private and public hospitals and cancer centres across eight Asian countries. It found that, one year after diagnosis, 29% had died and nearly half (48%) had suffered financial catastrophe, defined as having to pay more than 30% of their annual income in healthcare costs (BMC Medicine 2015, 13:190). The fact is that out-of-pocket expenditures are ruining families. In many countries social health insurance, such as AUGE in Chile and RSBY in India, are also not keeping up with what it actually costs to deliver good basic cancer care in the public sector. A radical overhaul is urgently needed, but with so many competing needs, cancer’s place in universal health coverage is not assured. The last paradox reflects a deep-seated failure to square trade and investment liberalisation with the needs of public health. The evidence is overwhelming that these are serious drivers of the burden of non-communicable diseases, yet the proliferation of bilateral and regional preferential trade agreements, without any in-built public health protection, will simply drive up cancer risk factor exposure (Globalisation & Health 2014, 10:66). Development money today is being traded off against economic losses in health tomorrow. If this all sounds depressingly familiar, it is. Talking about the cost of cancer is really a debate about how we are going to manage to pay for our healthcare. High-income countries like France are now having to spend more than €11 billion every year to achieve the outcomes their populations enjoy. Yet the needs of the elderly and chronically ill are not being met (Value in Health 2010, 13:552–556). What we do know is that there is no straightforward investment–impact model. Increasing expenditure does not lead automatically to better outcomes without serious structural, organisational and cultural engineering (Nat Rev Clin Oncol 2016, 13:137). Irrespective of base funding, too much cancer care is poor value or the focus of corruption. However, just adopting high-income mechanisms for priority setting does not work. Context matters too much, and different ideological and normative values will need very different economic and fiscal strategies, as Thai colleagues have pointed out (Value in Health 2009, S26–S30). But this is not an excuse for ignoring the basic building blocks. Fund your health system properly. Invest in a strong public sector system for caring for cancer patients, and protecting them financially. And ruthlessly ensure the quality and fiscal probity of services from both public and private sector.


In his last two State of the Union addresses, President Barack Obama has focused on the need to deliver innovative solutions to improve human health, through the Precision Medicine Initiative in 2015 and the recently announced Cancer Moonshot in 2016. Precision cancer care has delivered clear patient benefit, but even for high-impact medicines such as imatinib mesylate (Glivec) in chronic myeloid leukaemia, the excitement at the success of this practice-changing clinical intervention has been somewhat tempered by the escalating price of this ‘poster child’ for precision cancer medicine (PCM). Recent studies on the costs of cancer drugs have revealed significant price differentials, which are a major causative factor behind disparities in the access to new generations of immunological and molecularly targeted agents. In this perspective, we will discuss the benefits of PCM to modern cancer control, but also emphasise how increasing costs...
are rendering the current approaches to integrating the paradigm of PCM unsustainable. Despite the ever increasing pressure on cancer and health care budgets, innovation will and must continue. Value-based frameworks offer one of the most rational approaches for policymakers committed to improving cancer outcomes through a public health approach.

Cancer is the primary cause of premature death in 28 of 53 European nations [40]. The aging patient demographic means that the incidence of cancer is on an upward trajectory and as such will place an ever increasing burden on health and social welfare systems in Europe. The premature morbidity and mortality associated with cancer also represents a significant economic cost to our labour force, due to lost productivity for our society. Thus, it is vital that we continue to employ discovery science to unlock the complexities that transform a normal cell into a cancer cell and use this information to inform preventative medicine as well as interventional treatment strategies. But it is also incumbent on us to ensure that the solutions that we develop are accessible to all members of our society, not just those who can pay the market price. Thus, in crossing the ‘Value Rubicon’, we must ensure that our processes to define value are fair and transparent and deliver equitable solutions that have a meaningful impact on outcomes, and are affordable, thus maximising their ability to be adopted by health care professionals. Optimising the value of innovation within cancer control pathways will ultimately provide the best standard of care for our patients.

May 2016


Evidence suggests that a considerably large proportion of cancer patients are affected by treatment-related financial harm. As medical debt grows for some with cancer, the downstream effects can be catastrophic, with a recent study suggesting a link between extreme financial distress and worse mortality. At least three factors might explain the relationship between extreme financial distress and greater risk of mortality: 1) overall poorer well-being, 2) impaired health-related quality of life, and 3) sub-par quality of care. While research has described the financial harm associated with cancer treatment, little has been done to effectively intervene on the problem. Long-term solutions must focus on policy changes to reduce unsustainable drug prices and promote innovative insurance models. In the mean time, patients continue to struggle with high out-of-pocket costs. For more immediate solutions, we should look to the oncologist and patient. Oncologists should focus on the value of care delivered, encourage patient engagement on the topic of costs, and be better educated on financial resources available to patients. For their part, patients need improved cost-related health literacy so they are aware of potential costs and resources, and research should focus on how patients define high-value care. With a growing list of financial side effects induced by cancer treatment, the time has come to intervene on the “financial toxicity” of cancer care.

The term “financial toxicity” has been used to describe the harmful personal financial burden faced by patients receiving cancer treatment (1). As with any adverse effect of cancer treatment, the experience of financial toxicity is diverse and can range from subjective distress resulting from monthly copayments that prompt changes in household spending to personal bankruptcy. But what is the scale of the problem? Current evidence suggests that a considerably large proportion of patients is affected by treatment-related financial harm. According to the Centers for Disease Control and Prevention, one in three Americans experiences financial burden as a result of medical care (2). The burden is greater for cancer patients, who pay more out-of-pocket for care than those with other chronic illnesses (3). Indeed, 13% of nonelderly cancer patients spend at least 20% of their income on out-of-pocket expenses (3). Fifty percent of Medicare beneficiaries with cancer pay at least 10% of their income towards cancer treatment—related out-of-pocket costs (4). In other words, half of elderly cancer patients are underinsured. When framed this way, the true scale of the problem is evident.

Despite the millions who now have access to care as a result of the Patient Protection and Affordable Care Act (ACA), there is little evidence that cancer care is any more affordable than prior to the ACA. The Kaiser Family Foundation conducted a nationally representative survey of consumer finances to estimate the proportion of households that can afford cost-sharing requirements of the ACA (5). The study found that many households—particularly those with low incomes—lack the resources to cover the standard cost-sharing demands of today’s insurance plans available on the exchanges. For example, only 53% of all households had sufficient funds on hand to pay a median, mid-range, annual deductible of $2400 per family, and only 45% could pay a median, high-range deductible of $5000. This figure is particularly important as out-of-pocket costs for cancer care approach $5000 per year (3,4). Keeping in mind that cancer treatment is likely to span more than one calendar year, it is not difficult to envision how even well-insured cancer patients find themselves struggling with medical debt.

As medical debt grows for some with cancer, the downstream effects can be catastrophic. Analyzing population-based data from Western Washington State, Ramsey et al. found that having a cancer diagnosis was associated with a 2.65-times greater likelihood of declaring personal bankruptcy. Recently, those investigators re-examined the same data to determine whether personal bankruptcy was associated with poorer health outcomes. They compared a sample of patients with cancer who declared bankruptcy to a propensity-matched sample of patients with cancer who had not declared bankruptcy. They found that those cancer patients who declared bankruptcy had a 79% greater mortality risk than those who had not (6). This finding is striking as it is among the first to demonstrate a link between extreme financial
distress (manifested by a declaration of personal bankruptcy) and greater risk of mortality (7). However, this finding also begs the question: Why does this relationship exist?

How Does Financial Toxicity Worsen Outcomes?

At least three factors might explain the relationship between extreme financial distress and greater risk of mortality (Figure 1): 1) poorer subjective well-being, 2) impaired health-related quality of life, and 3) sub-par quality of care. The initial research in cancer treatment–related financial toxicity focused primarily on the relationship between financial burden and the resultant poorer subjective well-being of cancer patients. Subjective well-being has been defined as “different valuations that people make regarding their lives, the events happening to them, their bodies and minds, and the circumstances in which they live” (8). Numerous studies have found that because of high out-of-pocket expenses cancer patients and their caregivers face considerable detriment to their subjective well-being (9–11). To defray expenses, they are at risk of cutting back leisure activities, spending less on food and clothing, and working longer hours (1,12). These lifestyle changes are challenging for most people and even more so for those facing a new diagnosis of cancer. Beyond being challenging, evidence suggests that poor subjective well-being might impact health outcomes including survival. Three factors that might explain the relationship between extreme financial distress and greater risk of mortality.

Second, financial distress might worsen survival because of its impact on health-related quality of life (HRQOL), which is distinct from subjective well-being. HRQOL is defined as aspects of quality of life that relate specifically to a person’s health, including domains of physical, social, and mental functioning (15). At least two large studies have suggested an association between cancer treatment–related financial burden and poorer HRQOL. Fenn et al. studied data from 2108 cancer patients who participated in the National Health Interview Survey and found that compared with those with no financial hardship patients who reported “a lot” of financial problems due cancer care were more likely to report poor physical health, poor mental health, and less satisfaction with relationships (16). Importantly, greater financial hardship was the strongest independent predictor of reporting worse HRQOL. Another analysis of data from the demographically representative Cancer Care Outcomes Research and Surveillance Consortium study (17) found that among 1000 patients with lung or colorectal cancer high financial burden was associated with worse self-reported HRQOL (18). Because several studies have suggested that poor HRQOL is an independent negative prognostic marker for cancer patients (19,20), poor HRQOL might help explain the risk of shortened survival for patients with extreme financial distress.

Three factors that might explain the relationship between extreme financial distress and greater risk of mortality. First, higher out-of-pocket costs can harm the quality of cancer care. The effect of financial burden on adherence to medications is perhaps the most convincing contributor to the relationship between financial burden and mortality. As cost sharing rises—in the form of greater copayments for prescription medication—patients with cancer are at risk of facing large bills as a result of their anticancer therapy. While the price of all chemotherapy, oral and IV, has risen dramatically over the past few decades (21), cost-related nonadherence is a concern as patients are faced with the more immediate decision of paying the copayment for the oral chemotherapy prescription or forgoing the treatment. Evidence suggests patients are experiencing difficulty in keeping up with those copayments. Neugut et al. found that among women receiving adjuvant hormonal breast cancer therapy higher monthly copayments ranging from $30 to $90 for those drugs were associated with greater odds of noncompliance (22). And greater noncompliance with hormonal therapy has been associated with increased mortality (23). Hormonal therapy for breast cancer is not the only example of high out-of-pocket costs leading to nonadherence. Among patients with chronic myeloid leukemia (CML), Dusetzina et al. found that those with higher copayments, classified as greater than $53 per month, were 70% more likely to discontinue imatinib within six months of initiation (24). Disturbingly, these studies suggest that relatively small changes to patients’ budgets—in the range of less than $100 per month—can induce nonadherence to potentially life-saving drugs. A growing body of evidence supports the existence of financial toxicity resulting from cancer treatment, and recent research suggesting a link between financial toxicity and greater risk of mortality is compelling. Research on patient financial burden should focus on verifying the detrimental impact of financial distress on cancer-related outcomes, including mortality. More work can be done to better explain the relationship between financial distress and worse outcomes, with efforts to differentiate aspects of financial burden that contribute most to distress, including direct costs like coinsurance and indirect costs like time off work. While these descriptive studies are important, intervention work should proceed in parallel.

How Can We Intervene Today?

With a growing list of financial side effects induced by cancer treatment, the time has come to intervene. To reduce the personal financial burden of cancer treatment, interventions should be developed that focus on all involved parties. Others have written eloquently on how the pharmaceutical industry has a responsibility to lower the price of drugs, especially because drugs entering the market are priced with little correlation to improvement in outcomes (25,26). The government could play a role if, for example, the Centers for Medicare and Medicaid Services was allowed to negotiate prices with drug makers, which some argue would result in lower drug prices in the United States (26). Another policy initiative could promote pricing based on outcome, where inadequate response to a drug would result in a refund (27). Payers must play a role as well. A greater proportion of costs has been shifting to patients in the form of higher premiums, deductibles, and tiered formularies. Average worker contributions to premiums have doubled since 1999, and over the past six years the average annual deductible has more than doubled, from $584 in 2006 to $1217 in 2014 (28). To prevent nonadherence because of cost sharing, payers should consider value-based insurance design that reduces or eliminates cost sharing for high-value treatment (like imatinib for CML).

Realistically, any policy intervention directed at manufacturers or payers is unlikely to be implemented anytime soon. If we are to intervene on the financial toxicity of cancer treatment today, we must look to the provider and patients. The goal of
enhancing shared decision-making to reduce costs has been championed by the Institute of Medicine as a high priority for oncologists (30,31), but this will require a paradigm shift with three components. First, to intervene today on high patient costs oncologists should focus on the value of care delivered. Specifically, this means discouraging use of interventions that have little benefit but high cost. Vocal clinicians focused on value can influence drug pricing, as evidenced by the case of ziv-afibercept. (32). The drug, indicated for the treatment of metastatic colorectal cancer, was introduced at twice the price of existing treatment but without any comparative effectiveness data that supported its higher price. After the well-known, highly publicized effort by Memorial Sloan-Kettering physicians to not prescribe ziv-afibercept for the treatment of metastatic colorectal cancer, the manufacturer, Sanofi, reduced the price of the drug to match prices of existing treatment. More recently, when the price of a toxoplasmosis drug was raised by 5000%, media attention generated by vocal infectious disease doctors forced a price reduction within days of the initial price hike (33).

Second, oncologists must initiate the conversation. As oncologists, we need to focus more on goals of care discussions early in the treatment course (34). Specific to costs, studies suggest physicians are interested in discussing costs with patients, but few feel comfortable or prepared to have that discussion (35,36). Yet simply asking patients if they have difficulty paying for their medical care is an important means for oncologists to ally themselves with patients. Many patients seek engagement with oncologists regarding costs but are unsure how to broach the topic in clinic. For example, our research found that half of patients surveyed were interested in discussing their cost burden with their oncologist, but only 19% followed through with a cost discussion (37). When asked what barriers hindered a cost discussion, 28% of patients stated they avoided the discussion because they wanted the best care regardless of cost. These data suggest some patients are concerned they might receive lesser quality care if they bring up costs with their oncologist. However, in most cases cost can be addressed without changing any treatment but rather by directing patients to financial resources and advocating on behalf of the patient with the insurance company (38). Hence, when appropriate and desired, communication-based interventions could promote discussions about out-of-pocket costs between patients and their physicians.

Third, if patients are prompted to broach the topic of costs, physicians must be prepared for the discussion. As such, interventions must focus on educating physicians on how to engage patients regarding value in cancer care. Oncologists know little about the out-of-pocket costs incurred from the treatments prescribed. One tool that presents a step in the right direction is the American Society of Clinical Oncology’s Value Framework, which calculates a Net Health Benefit score and displays it alongside potential costs to the patient (39). Even if oncologists do not know how much a prescription will cost, other members of the healthcare delivery team can find out. Pharmacists and financial counselors can check insurance coverage before patients leave clinic with expensive prescriptions and can identify financial resources for patients early in the course of care.

Fourth, to reduce financial toxicity, patients have a role to play. Patient-level interventions must focus on improving patients’ conceptual knowledge of health insurance and finance, also known as cost-related health literacy (40). According to the National Assessment of Adult Literacy, nearly 80 million Americans have health literacy that is considered “basic” or “below basic” (41). Specific to cost-related health literacy, Americans also fare poorly when it comes to basic knowledge about health insurance. In one national study, only 42% of participants could accurately describe a deductible, and only half were aware of the new exchanges established by the Affordable Care Act (42). Because of limited cost-related health literacy, insured patients are often surprised by the costs they face upon starting cancer treatment, and few know where to turn for help (43). Interventions should focus on educating patients on the basics of health insurance, potential costs they might face during treatment, and available resources like patient assistance programs. In addition to cost-related health literacy, research should focus on how patients define value and what aspects of their care they value most, relative to their personal experience. Without this work, value discussions initiated by oncologists will have limited effectiveness.

Financial toxicity is a concern for a growing proportion of patients, with half of all Medicare patients with cancer at risk of being underinsured. We now have an evidence-based list of harms that patients experience as a result of cancer treatment–related out-of-pocket costs. A recent study suggests that extreme financial distress as manifested by personal bankruptcy might be associated with worse mortality in cancer patients. That relationship between financial distress and worse outcomes is likely explained by the impact of cancer-related expenses on patient well-being, health-related quality of life, and adherence to anticancer therapy. Research should focus on verifying and further describing this relationship. Long-term solutions must include policy shifts involving how we set prices, negotiate prices, and insure patients. But for more immediate solutions, interventions should focus on the oncologist and patient. To reduce financial toxicity, we should intervene today.

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**Evolving Approaches in Research and Care for Ovarian Cancers A Report From the National Academies of Sciences, Engineering, and Medicine**


Most women with ovarian cancer present at an advanced stage, when the case-fatality rate is high. Approximately 22,280 women are diagnosed with ovarian cancer in the United States each year; 60% are classified as advanced stage, and the overall 5-year survival for these women is 28%. Reliable approaches for early detection of ovarian cancer have thus far been difficult to establish. The recently released report from the Institute of Medicine of the National Academies of
OVARIAN CANCER IS NOT ONE DISEASE

Recent evidence suggests that most ovarian cancers do not arise in the ovary, as had been thought for decades. Instead, the most common and aggressive form of ovarian cancer, high-grade serous carcinoma (HGSC), is now thought to arise predominantly in the distal end of the fallopian tube. Other forms of ovarian cancer, including endometrioid, clear cell, and low-grade serous, likely arise from different sites and cells of origin including ovarian cysts and endometriosis, emphasizing the heterogeneity involved in the etiology and risk of ovarian cancer. Until this time, clinicians and researchers have combined these varied subtypes of ovarian cancer into one disease, which has further complicated efforts toward understanding basic biology, prevention, and treatment. The Academies’ committee recommends that research should account for the varied types of ovarian cancer and that a high priority should be given to the elucidation of the origins and pathogenesis of each subtype. To help reach this goal, classification schemes should reflect the morphologic and molecular heterogeneity of ovarian cancers, and standardized taxonomy should be widely adopted. To achieve this consensus, multiple stakeholders will need to address these complex issues in a collaborative, iterative, and dynamic process.

A CALL FOR EXPANDED SCREENING AND PREVENTION RESEARCH

To date, combined-modality screening with the CA-125 tumor marker and transvaginal ultrasonography have not been able to reliably detect ovarian cancer at early stages, when cure rates are remarkably high. The largest and recently reported screening trial from the United Kingdom (UKCTOCS) involved 202,638 women and used multimodality screening (MMS) with an algorithm to assess increases in CA-125 levels, which served as a trigger for transvaginal sonography as a secondary screen for abnormal biomarker results. This approach resulted in fewer unnecessary operations than sonography alone (2 per cancer diagnosed in the MMS group vs 10 in the sonography group) and a downstaging of disease with an increase in the detection of early-stage ovarian cancer (40% vs 24%). The 15% relative reduction in mortality seen in the MMS group and 11% in the sonography group were not significantly different than no screening in the primary analysis based on mortality rates of 0.29%, 0.30%, and 0.34% for the MMS, sonography, and no screening groups, respectively. The data suggested that most of the benefits of screening would occur between 7 and 14 years after initiation. Approximately 640 women would need to be screened annually for nearly 14 years to prevent 1 death from ovarian cancer. Further follow-up will be needed before definitive conclusions can be made regarding the efficacy of this approach to screening. Therefore, the committee recommended that future strategies should extend beyond the current biomarkers and imaging modalities to reflect the pathobiology of each ovarian cancer subtype.

For more than 2 decades, it has been known that germline mutations in BRCA1 and BRCA2 are associated with an increased risk of breast and ovarian cancers. Professional societies and other organizations recommend that all women with invasive ovarian cancer undergo genetic testing for mutations in these genes. The primary purpose of this genetic testing is to identify unaffected family members who may be at increased risk for ovarian cancer and could use preventive measures such as risk-reducing surgery or chemoprevention to decrease the risk of developing the disease. Secondly, test results may help to stratify patients for newer targeted treatment approaches such as PARP (poly [ADP-ribose] polymerase) inhibition. However, many women with HGSC do not receive genetic counseling or undergo genetic testing owing to lack of knowledge by patients and clinicians or complex and inconsistent referral criteria, preventing the full benefit of risk reduction to be realized at present. Innovative strategies should be developed to increase the uptake of genetic testing and to share results among other at-risk family members. New approaches for surgical (e.g., salpingectomy) and nonsurgical risk reduction should also be developed and studied in the context of risk-benefit balance.

TREATMENTS SHOULD BE STANDARDIZED AND DISSEMINATED

Over several decades, standards of care have been defined for the treatment of advanced-stage HGSC that include initial primary cytoreductive surgery followed by combination cytotoxic chemotherapy, often delivered intraoperatively for patients whose disease is completely resected. Although treatment consistent with accepted guidelines has been associated with improved outcomes, less than half of patients with HGSC receive this treatment. To ensure the consistent implementation of current standards of care, studies should be directed toward reducing disparities in health care delivery and outcomes. Since no single model will be applicable to all patients and health care settings, additional research will be required to determine the best timing and type of initial surgery for newly diagnosed women, including the appropriate use of neoadjuvant chemotherapy approaches. In addition, a better understanding of the mechanisms of disease recurrence and drug resistance will be essential to improving patient outcome. Exciting recent data have now paved the way for more effective pharmacologic and nonpharmacologic therapies and combinations of therapies that consider the unique biology and clinical course of ovarian cancer. In particular, immunologic and molecularly driven...
approaches specific to the different ovarian cancer subtypes performed by interdisciplinary teams should lead to efficient and information-rich clinical studies. Owing to the relative rarity of ovarian cancer and the distinct biology of the various subtypes, it will be important to develop and support more robust collaborative consortia to assess these new therapies. Throughout the disease course, women will require long-term active disease management through supportive care and self-management strategies. The committee recommends that research efforts be directed toward identifying factors that put patients at high risk for poor outcomes and overcoming barriers to the systematic assessment of psychosocial effects of disease and treatment. Furthermore, complex factors influence the adoption of research results into clinical care, including the transfer of knowledge to all appropriate stakeholder groups. Effort should be directed toward the rapid dissemination and implementation of evidence-based information and practices to patients, families, physicians and other health care professionals, and advocates, using existing and newly developed dissemination modalities. Although progress has been made in understanding ovarian cancers, especially over the last decade, additional research focused on the origins and mechanisms of disease will help to shape current and future approaches to prevention, screening and early detection, and treatment. Improved communication among patients, physicians and other clinicians, and researchers is also needed to recognize ovarian cancer as a compendium of many types of cancer involving the ovary. These efforts will help reduce the burden of ovarian cancer and result in improved survivorship and survival.


Abstract The bony pelvis of adult humans exhibits marked sexual dimorphism, which is traditionally interpreted in the framework of the “obstetrical dilemma” hypothesis: Giving birth to large-brained/large-bodied babies requires a wide pelvis, whereas efficient bipedal locomotion requires a narrow pelvis. This hypothesis has been challenged recently on biomechanical, metabolic, and biocultural grounds, so that it remains unclear which factors are responsible for sex-specific differences in adult pelvic morphology. Here we address this issue from a developmental perspective. We use methods of biomedical imaging and geometric morphometrics to analyze changes in pelvic morphology from late fetal stages to adulthood in a known-age/known-sex forensic/clinical sample. Results show that, until puberty, female and male pelves exhibit only moderate sexual dimorphism and follow largely similar developmental trajectories. With the onset of puberty, however, the female trajectory diverges substantially from the common course, resulting in rapid expansion of obstetrically relevant pelvic dimensions up to the age of 25–30 y. From 40 y onward females resume a mode of pelvic development similar to males, resulting in significant reduction of obstetric dimensions. This complex developmental trajectory is likely linked to the pubertal rise and premenopausal fall of estradiol levels and results in the obstetrically most adequate pelvic morphology during the time of maximum female fertility. The evidence that hormones mediate female pelvic development and morphology supports the view that solutions of the obstetrical dilemma depend not only on selection and adaptation but also on developmental plasticity as a response to ecological/nutritional factors during a female’s lifetime.

Significance The obstetrical dilemma hypothesis states that the human female pelvis represents a compromise between designs most suitable for childbirth and bipedal locomotion, respectively. This hypothesis has been challenged recently on biomechanical, metabolic, and biocultural grounds. Here we provide evidence for the pelvis’ developmental adaptation to the problem of birthing large-headed/large-bodied babies. We show that the female pelvis reaches its obstetrically most adequate morphology around the time of maximum fertility but later reverts to a mode of development similar to that of males, which significantly reduces the dimensions of the birth canal. These developmental changes are likely mediated by hormonal changes during puberty and menopause, indicating “on-demand” adjustment of pelvic shape to the needs of childbirth.


Abstract Current sequencing methods are error-prone, which precludes the identification of low frequency mutations for early cancer detection. Duplex sequencing is a sequencing technology that decreases errors by scoring mutations present only in both strands of DNA. Our aim was to determine whether duplex sequencing could detect extremely rare cancer cells present in peritoneal fluid from women with high-grade serous ovarian carcinomas (HGSOCs). These aggressive cancers are typically diagnosed at a late stage and are characterized by TP53 mutations and peritoneal dissemination. We used duplex sequencing to analyze TP53 mutations in 17 peritoneal fluid samples from women with HGSOC and 20 from women without cancer. The tumor TP53 mutation was detected in 94% (16/17) of peritoneal fluid samples from women with HGSOC (frequency as low as 1 mutant per 24,736 normal genomes). Additionally, we detected extremely low frequency TP53 mutations (median mutant fraction 1/13,139) in peritoneal fluid from nearly all patients with and without cancer (35/37). These mutations were mostly deleterious, clustered in hotspots, increased with age, and were more abundant in women with cancer than in controls. The total burden of TP53 mutations in peritoneal fluid distinguished cancers from controls with 82% sensitivity (14/17) and 90% specificity (18/20). Age-associated, low frequency TP53
mutations were also found in 100% of peripheral blood samples from 15 women with and without ovarian cancer (none with hematologic disorder). Our results demonstrate the ability of duplex sequencing to detect rare cancer cells and provide evidence of widespread, low frequency, age-associated somatic TP53 mutation in noncancerous tissue.

**Significance**  The detection of rare tumor-specific somatic mutations in “liquid biopsies” is limited by the high error rate of DNA sequencing technologies. By sequencing peritoneal fluid from women with high-grade serous ovarian cancer, we demonstrate that duplex sequencing, currently the most accurate sequencing technology, is able to detect one cancer cell among tens of thousands of normal cells. This unprecedented sensitivity also revealed a striking prevalence of extremely low frequency TP53 mutations in normal tissue. Women with and without cancer harbored TP53 mutations of pathogenic consequences, both in peritoneal fluid and peripheral blood. These mutations likely represent a premalignant mutational background that accumulates in cancer and aging.

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**Screening with CRISPR: Ever-improving CRISPR-based tools are already ripe for large-scale genetic screens.**

KR Chi  The Scientist  June 1, 2016  http://www.the-scientist.com/?articles.view/articleNo/46127/title/Screening--with-CRISPR&utm_campaign=NEWSLETTER_TS_The-Scientist-Daily_2016&utm_source=hs_email&utm_medium=email&utm_content=31132325&_hsenc=p2ANqtz-8C114kVZsdCHSCrAi-XT4Xg8tZpDGGdCjE-8C114kVZSdCHSCrAi-XT4Xg8tZpDGGdCjE-

With gene editing—and in particular, the CRISPR/Cas9 system—scientists are in some sense building a shiny new car at the same time they are taking it for a spin. And it’s been a joyride. CRISPR/Cas9, as it was originally conceived for gene editing in late 2012, makes cuts at specific locations along DNA with help from a short stretch of guide RNA that takes the Cas9 endonuclease to a specific site. Increasingly, groups are applying this technology in large-scale genetic screens—for example, to identify mutations that drive treatment resistance in cancer, or to rapidly assess drug targets. RNA interference doesn’t come close to what CRISPR/Cas9 can do for genetic screens, both in specificity and in efficiency. At the same time, researchers such as Traver Hart of the MD Anderson Cancer Center are working to further understand the power and the limitations of CRISPR/Cas9 and what it does in, for example, uncharacterized human cell lines. The CRISPR/Cas9 toolbox continues to expand. Disabled versions of Cas9, pioneered by the Broad Institute’s Feng Zhang and by other groups, bind to the genome and either halt or enhance transcription, depending on the application. Zhang and others are engineering the Cas9 enzyme to make it more specific and are discovering new gene-editing proteins, too. Hart and Zhang discuss their work on the frontlines of CRISPR/Cas9 development and application in “Genetic Screens: A Route to Rapid Progress in Disease Targeting and Drug Development,” a webinar from The Scientist. The following pages contain highlights from their presentations.

**ADVANCES IN CRISPR TECHNOLOGY** Feng Zhang

MIT’s Feng Zhang discussed engineering the Streptococcus pyogenes Cas9 protein to improve specificity (Science, 351:84-88, 2016). The Cas9 endonuclease can induce off-target mutations when pairing between DNA and the guide RNA is not perfect, which makes it less than ideal for precision editing of the genome in clinical settings. DNA strands need to separate to accommodate the Cas9 protein. Structural analysis by Zhang’s group revealed a positively charged groove on the Cas9 protein at the spot where the negatively charged non-target DNA fits. “We thought maybe if we [neutralized] some of these positive charges then we could weaken the stabilization and therefore make [Cas9] more specific,” Zhang says. They tried this approach using guide RNAs that have been known to land on particular off-target sites. The group created 32 single-point mutants of Cas9 and targeted each of them to the gene EMX1 via its validated specific guide. Five of the Cas9 mutants were able to preserve the on-target activity and reduce the cuts at off-target sites by tenfold. Then the team tried using the mutated Cas9s to cut another gene, VEGFA (whose guide is known to cut at two previously identified off-target sites). Although all of the mutated Cas9s reduced off-target effects, the group thought that they should combine mutations to make the Cas9 even more specific, Zhang says. They generated two different mutants with triple-point mutations and “found we were able to preserve the on-target activity and then even further reduce the off-target activity so that we no longer detect it,” he says. Zhang calls these enhanced-specificity Cas9 proteins “eSpCas9 variants.” Testing numerous guide RNAs with one single-point and one triple-point mutant eSpCas9, the scientists found that both of them edited on-target sites with similar efficiency. Although there were some variations in efficiency with different guides, “on average, [the mutants] were on par with the wild-type Cas9,” Zhang says. By trying various mutations of guide RNAs in combination with the wild-type Cas9, Zhang’s group has found that there is a so-called “seed region” at the 3’ end of the guide that confers specificity. In contrast, the new eSpCas9 variants extend this seed region to include the entire guide. And the group is continuing to make the system even more specific, says Zhang. Discovering unknown gene function using CRISPR One exciting feature of the CRISPR system is how specific guide RNAs are, Zhang says. This makes it possible to generate a lentivirus library of CRISPR guides that target every gene or multiple sites within a given gene. These are then transduced into cell lines, resulting in pools of cells in which individual genes have been either inactivated (Science, 343:84-87, 2014; Cell, 160:1246-60, 2015) or activated (Nature, 517:583-88, 2015). To show the power of these screens, Zhang’s group addressed treatment resistance to melanoma. The BRAF V600E is a well-known cancer mutation that is treated by the US Food and Drug Administration–approved drug vemurafenib (Zelboraf). However, resistance arises in rapidly mutating cells, and by 24 weeks of treatment the tumors return. “We thought this might be an opportunity for us to apply a genome-scale library to see what are the
genes—when you either turn them on or turn them off—that would render the tumor cell resistant to vemurafenib," Zhang says. Zhang’s CRISPR knockout library uses guides that target all the conserved coding exons in the genome. “When designing these kinds of screening experiments, we always use multiple guides so that we have some redundancy and also to be able to know that the effect of any single guide is not due to an off-target modification," he adds. They then tried to validate their new candidates and compare their results to a previously conducted RNAi screen (Cancer Discov, 3:350-62, 2013), finding that they could confirm several of their top CRISPR hits confer vemurafenib resistance; in the RNAi screen, only the top hit was confirmed. Gain-of-function CRISPR-based screens developed by Zhang’s group have also enabled the study of vemurafenib resistance. Zhang calls this new CRISPR-based tool for activating genes the synergistic activation mediator, or SAM, which his team showed can activate 12 different genes that they had had trouble switching on using older methods. “And for many genes where the old system couldn’t really activate, the new system is able to activate transcription by 100- or 1,000-fold,” Zhang says. Zhang’s lab is working to further expand the CRISPR editing toolbox by identifying additional enzymes useful for genome editing. For example, last fall they discovered Cpf1, another DNA endonuclease that is equipped with different cutting actions that may make it more useful in some cases (Cell, 163:759-71, 2015). The group also described additional CRISPR/Cas systems C2c1, C2c2 and C2c3 (Mol Cell, 60:385-97, 2015), and is studying their mechanisms.

Cancer Targeting Using Genetic Screens in Human Cell Lines Traver Hart

RNAi-based screens have made genome-scale perturbation screening in human cells possible. But an incomplete understanding of the biology of RNAi and of the data generated by such screens has led to some false starts in the field, says Traver Hart of MD Anderson Cancer Center, citing a 2012 Science perspective that expounded on these issues and argued for more-sophisticated approaches to studying mammalian gene function (337:421-22, 2012). Working in Jason Moffat’s lab at the University of Toronto, Hart himself helped define a set of gold standards that can be used to evaluate the quality of both RNAi and CRISPR genetic screens (Mol Syst Biol, 10:733, 2014), just as the first two large-scale CRISPR knockout screens in human cell lines were published (Science, 343:84-87, 2014; Science, 343:80-84, 2014). Using the HCT116 cell line (derived from a human colon cancer) as an example, Hart showed that CRISPR screens are not only more sensitive but they also do not generate additional background errors. How do CRISPR screens represent such an improvement over RNAi? CRISPR screens work across a “whole range of biologically meaningful gene expression [levels], whereas shRNA [short hairpin RNA] seems to work really well only at very high expression levels,” Hart says. “This was information that we didn’t have from the shRNA data until we had something better to compare it to. So, we didn’t know what we didn’t know. This is one way that we’re quite sure that CRISPR has completely revolutionized this field of genetic screening.” Hart’s group recently generated the Toronto KnockOut (TKO) library, a second-generation library of lentiviral-encoded guide RNAs that target 17,661 human protein-coding genes. They conducted fitness screens (also known as essentiality screens) in four cancer cell lines and one normal cell line. In their study, they defined a fitness or essential gene as one whose perturbation diminishes cell growth and proliferation. The team detected nearly 1,600 core fitness genes (Cell, 163:1515-26, 2015). “That number is astonishing to anyone who’s done shRNA or RNAi work (where that number is in the low hundreds),” Hart says. What Hart and his colleagues are primarily interested in, however, is what genes are differentially required across different cell lines or genetic backgrounds. Knowing the genotypes of the cell lines they’ve studied so far helps them make predictions. For example, the colon cancer–derived DLD1 and HCT116 cell lines both have KRAS driver mutations, suggesting that the downstream MAPK pathway is active, and this prediction bears out in their screens. To better understand context-specific vulnerabilities in each cell line, Hart subtracted the core essentials and conducted functional enrichment tests on their remaining context- specific essentials. This revealed a unique signature of processes required for optimal fitness, he says. These studies have revealed some surprises: cell lines with similar genetic profiles can differ in their fitness profiles. For instance, both DLD1 and HCT116 carry oncogenic KRAS mutations, yet the gene for epidermal growth factor receptor, a cell-surface receptor linked with numerous cancers, including colorectal cancer, and its molecular partners are hit in only the DLD1 line. In a separate, as-yet-unpublished line of work, Hart’s group conducted a follow-on screen in HPAF-II pancreatic cancer cells. The genetic screen detects numerous secondary processes involved in cell proliferation—for example, posttranslational modifications and receptor endocytosis. “In many senses, this is an embarrassment of riches you get from one of these screens,” Hart says. In addition, the screens fingered specific members of receptor families—1 of 10 in the frizzled receptor family and 1 of 17 Wnt ligands—as essential. “Not only do we get the breadth of the pathways and processes that are required to support wild-type growth in this cell line, but we also get very specific, potentially actionable targets,” he says. Core essential genes in cancer cell lines can also be explored as therapeutic targets. In 2012, Dana-Farber Cancer Institute researchers showed that when mutating cancers delete regions coding for tumor suppressor genes they also remove various “passenger” genes that do not directly play a role in cancer but that may leave tumor cells vulnerable to additional specific insults (Cell, 150:842-54, 2012). This concept has since been dubbed “collateral lethality” and is believed by Hart and others to be an opportunity for therapy (Trends Cancer, 1:161-73, 2015). Deleting core essential genes in the vicinity of a tumor suppressor gene presents a therapeutic window, Hart says. For example, POLR2A is a core essential gene that encodes an RNA polymerase subunit, and a copy of the gene is almost always co-deleted with the well-known tumor suppressor gene TP53 in ovarian cancer. Last year, Xiongbin Lu’s team at MD Anderson showed that TP53 loss sensitized colorectal cancer cells to polymerase inhibition (Nature, 520:697-701, 2015). The inventory of core essential genes will continue to grow, and sharpen, as more researchers conduct CRISPR screens, Hart says. “They are scattered all over the genome, and as idiosyncratic copy losses occur in tumors, any one of these might then become

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a therapeutic target,” he says. “This is a very exciting frontier for cancer research—not just the context sensitivity but also the core essentials are potential therapeutic targets.”

**USPSTF Declines to Make Recommendation on Routine Pelvic Exams in Draft Statement.** The U.S. Preventive Services Task Force said there is not enough evidence for it to make a recommendation either for or against conducting pelvic examinations to screen for various gynecologic conditions (e.g., candidiasis, ovarian cancer) in asymptomatic, nonpregnant adult women. The draft statement doesn’t include screening for cervical cancer, gonorrhea, or chlamydia. These are addressed in other USPSTF recommendation statements. In the absence of high-quality evidence to assess the balance of the exam’s benefits and risks, Dr. Robert L. Barbieri of NEJM Journal Watch Women’s Health offers this advice: “1) perform a pelvic exam based on history for symptoms such as a vaginal discharge, abnormal uterine bleeding, pelvic pain, etc.; 2) perform a periodic complete pelvic examination while collecting specimens for screening for cervical dysplasia and cancer, gonorrhea, and chlamydia; 3) consider periodic screening pelvic examinations every 1 to 3 years for women 21–64 years of age to assess for diseases of the vulva, vagina, cervix, uterus and adnexa; and 4) periodic screening pelvic examinations are not a high priority, unless indicated based on symptoms, for women younger than 21 years old or older than 65 years.”

**April 2016**

**Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones.** YA Ren, LK Mullany, Z Liu, A J. Herron, K-K Wong,* and JS Richards. Cancer Res April 15, 2016 76; 2206-18

http://cancerres.aacrjournals.org/content/76/8/2206.full

Mutations in the tumor protein p53 (TP53) are the most frequently occurring genetic events in high-grade ovarian cancers, especially the prevalence of the Trp53R172H-mutant allele. In this study, we investigated the impact of the Trp53R172H-mutant allele on epithelial ovarian cancer (EOC) in vivo. We used the Pten/KrasG12D–mutant mouse strain that develops serous EOC with 100% penetrance to introduce the mutant Trp53R172H allele (homolog for human Trp53R172H). We demonstrate that the Trp53R172H mutation promoted EOC but had differential effects on disease features and progression depending on the presence or absence of the wild-type (WT) TP53 allele. Heterozygous WT/Trp53R172H alleles facilitated invasion into the ovarian stroma, accelerated intraperitoneal metastasis, and reduced TP53 transactivation activity but retained responsiveness to nutlin-3a, an activator of WT TP53. Moreover, high levels of estrogen receptor α in these tumors enhanced the growth of both primary and metastatic tumors in response to estradiol. Ovarian tumors homozygous for Trp53R172H mutation were undifferentiated and highly metastatic, exhibited minimal TP53 transactivation activity, and expressed genes with potential regulatory functions in EOC development. Notably, heterozygous WT/Trp53R172H mice also presented mucinous cystadenocarcinomas at 12 weeks of age, recapitulating human mucinous ovarian tumors, which also exhibit heterozygous TP53 mutations (∼50%–60%) and KRAS mutations. Therefore, we present the first mouse model of mucinous tumor formation from ovarian cells and supporting evidence that mutant TP53 is a key regulator of EOC progression, differentiation, and responsiveness to steroid hormones.


https://www-clinicalkey-com.ezproxy.uky.edu/#/content/journal/1-s2.0-S0002937816000545

**Objectives** To determine the prevalence of occult pre-malignant or malignant uterine pathology at the time of laparoscopic surgery utilizing open uterine morcellation (OUM) for benign gynecologic disease and to identify preoperative risk factors.

**Materials and Methods** We conducted a multicenter, retrospective cohort study of women who underwent OUM for benign indications from January 2007 through February 2014 at three institutions. We collected demographic, preoperative and postoperative data from electronic medical records. The primary outcome was pre-malignant or malignant pathology at the time of OUM.

**Results** During this period, 1214 women underwent OUM and 14 (1.2%) were identified as having occult pre-malignant or malignant pathology. Among these cases, 6 (42.9%) had endometrial hyperplasia and 8 (42.8%) had an occult uterine malignancy. In the pre-malignant group there were 3 (50.0%) simple hyperplasia without atypia, 1 (16.7%) simple atypical hyperplasia, 1 (16.7%) complex hyperplasia without atypia and 1 (16.7%) endometrial intraepithelial neoplasia. Of the malignant cases, 5 (62.5%) had endometrial adenocarcinoma (EAC), 1 (12.5%) had low-grade endometrial stromal sarcoma (ESS), 1 (12.5%) had uterine tumor resembling ovarian sex cord tumor, and 1 (12.5%) had atypical leiomyoma. There was 1 case of endometrioid adenocarcinoma of the ovary (ovary not morcellated) that underwent a full staging procedure and intraperitoneal chemotherapy. All 5 cases of EAC underwent a second operative staging procedure. Four
had grade 1 EAC and required no adjuvant therapy. One case of grade 2 EAC required radiation, and the 1 case of grade 3 EAC with serous features had chemotherapy and vaginal cuff radiation. The cases of uterine tumor resembling ovarian sex cord tumor and low-grade ESS required a second operative procedure. The atypical leiomyoma occurred in a myomectomy specimen, and resulted in a total abdominal hysterectomy. All 8 cases are disease free as of last follow-up. There was no difference in preoperative characteristics including BMI, parity, history of hypertension, diabetes, breast cancer or smoking history between those with abnormal and normal pathology (P≥0.06 for all). The prevalence of uterine malignancy was 1.1% among premenopausal women and 1.2% among postmenopausal women. Six of the 7 patients with abnormal uterine bleeding (AUB) with subsequent pre-malignant or malignant pathology had a benign preoperative endometrial biopsy. None of the 7 women undergoing surgery for prolapse or fibroids without AUB had a preoperative biopsy.

**Conclusion** In this large cohort of women undergoing OUM for benign indications, the prevalence of endometrial adenocarcinoma was 0.41%, and 0.08% for low-grade ESS. There were no cases of leiomyosarcoma. We did not identify any potential risk factors for abnormal uterine pathology, though the small number of women with abnormal uterine pathology limits our power to detect potentially meaningful associations. One should consider further investigational procedures in women with a history of AUB and a negative endometrial biopsy who are undergoing uterine morcellation.


**OBJECTIVE:** To describe the association between postmenopausal estrogen-only therapy use and risk of ovarian carcinoma, specifically with regard to disease histotype and duration and timing of use.

**METHODS:** We conducted a pooled analysis of 906 women with ovarian carcinoma and 1,220 women in a control group; all 2,126 women included reported having had a hysterectomy. Ten population-based case–control studies participating in the Ovarian Cancer Association Consortium, an international consortium whose goal is to combine data from many studies with similar methods so reliable assessments of risk factors can be determined, were included. Self-reported questionnaire data from each study were harmonized and conditional logistic regression was used to examine estrogen-only therapy's histotype-specific and duration and recency of use associations.

**RESULTS:** Forty-three and a half percent of the women in the control group reported previous use of estrogen-only therapy. Compared with them, current or recent estrogen-only therapy use was associated with an increased risk for the serous (51.4%, odds ratio [OR] 1.63, 95% confidence interval [CI] 1.27–2.09) and endometrioid (48.6%, OR 2.00, 95% CI 1.27–2.09) histotypes. In addition, statistically significant trends in risk according to duration of use were seen among current or recent postmenopausal estrogen-only therapy users for both ovarian carcinoma histotypes (P trend <.001 for serous and endometrioid). Compared with women in the control group, current or recent users for 10 years or more had increased risks of serous ovarian carcinoma (36.8%, OR 1.73, 95% CI 1.26–2.38) and endometrioid ovarian carcinoma (34.9%, OR 4.03, 95% CI 1.91–8.49).

**CONCLUSION:** We found evidence of an increased risk of serous and endometrioid ovarian carcinoma associated with postmenopausal estrogen-only therapy use, particularly of long duration. These findings emphasize that risk may be associated with extended estrogen-only therapy use.

**Hormone Use After Nonserous Epithelial Ovarian Cancer: Overall and Disease-Free Survival**


**OBJECTIVE:** To evaluate whether hormone therapy (HT) after nonserous epithelial ovarian cancer is associated with a decrease in overall and disease-free survival.

**METHODS:** We conducted a retrospective cohort study. The Manitoba Cancer Registry and Drug Programs Information Network were searched to find all women with known nonserous epithelial ovarian, fallopian tube, or primary peritoneal cancer between 1995 and 2010 who had used HT after treatment. Women who did not receive treatment or had no follow-up were excluded.

**RESULTS:** Three hundred ninety-one patients met the inclusion criteria. Seventeen patients were excluded because the patients did not receive treatment for cancer, and 17 were excluded for lack of follow-up. A total of 94 women received HT after treatment, and 263 women did not. The average age was 57.8 years. In HT users younger than 55 years of age, disease-free survival is improved according to both the multivariable landmark analysis (n=68/145, adjusted hazard ratio 0.354, 95% confidence interval [CI] 0.17–0.74, P = .006) and the time-varying Cox regression analysis (n=42/158, adjusted hazard ratio 0.212, 95% CI 0.07–0.60, P = .004) when adjusting for International Federation of Gynecology and Obstetrics
stage and need for chemotherapy. There is no statistical difference in overall survival in this age group. No associations between HT use and overall survival or disease-free survival were found among women aged 55 years and older.

**CONCLUSION:** After treatment for nonserous epithelial ovarian cancer, hormone therapy is not associated with decreased disease-free or overall survival.


Data from screening trials indicate that a significant percent of asymptomatic women older than 50 years of age will develop ovarian abnormalities that are detectable by ultrasonography. Most of these abnormalities are benign, and many will resolve spontaneously. However, the risk of ovarian cancer, particularly in postmenopausal women, is of concern. The goal is to use a diagnostic and treatment algorithm that will reliably detect ovarian cancer at the earliest possible stage while limiting the number of women undergoing surgery for benign disease. The combination of morphology indexing and serum biomarker analysis can accurately predict the risk of malignancy in most ovarian tumors. Ovarian tumors with cystic or septate morphology are at minimal risk of malignancy and can be followed with serial ultrasonography evaluations, thereby avoiding the morbidity and cost of surgery. Complex or solid ovarian tumors with a high morphology index score, or those with increasing biomarker production, are at a high risk of malignancy, and patients with these tumors should be referred to a gynecologic oncologist for further evaluation and treatment.


**Importance** Germline mutations in BRCA1 and BRCA2 are relatively common in women with ovarian, fallopian tube, and peritoneal carcinoma (OC) causing a greatly increased lifetime risk of these cancers, but the frequency and relevance of inherited mutations in other genes is less well characterized.

**Objective** To determine the frequency and importance of germline mutations in cancer-associated genes in OC. Design, Setting, and Participants A study population of 1915 woman with OC and available germline DNA were identified from the University of Washington (UW) gynecologic tissue bank (n = 570) and from Gynecologic Oncology Group (GOG) phase III clinical trials 218 (n = 788) and 262 (n = 557). Patients were enrolled at diagnosis and were not selected for age or family history. Germline DNA was sequenced from women with OC using a targeted capture and multiplex sequencing assay.

**Main Outcomes and Measures** Mutation frequencies in OC were compared with the National Heart, Lung, and Blood Institute GO Exome Sequencing Project (ESP) and the Exome Aggregation Consortium (ExAC). Clinical characteristics and survival were assessed by mutation status.

**Results** Overall, the median (range) age at diagnosis was 60 (28-91) years in patients recruited from UW and 61 (23-87) years in patients recruited from the GOG trials. Patients with OC from UW were 1.6 years younger than those from GOG trials. A higher number of black women were recruited from the GOG trials (7.7% vs 1.4%; P < .001). A higher proportion of fallopian tube carcinomas (11.3% vs 5.7%; P < .001); stage I and II disease (14.6% vs 0% [GOG trials were restricted to advanced-stage cancer]); and nonserous carcinomas (29.9% vs 13.1%, P < .001). Of 1915 patients, 280 (15%) had mutations in BRCA1 (n = 182), or BRCA2 (n = 98), and 8 (0.4%) had mutations in DNA mismatch repair genes. Mutations in BRIP1 (n = 26), RAD51C (n = 11), RAD51D (n = 11), PALB2 (n = 12), and BARD1 (n = 4) were significantly more common in patients with OC than in the ESP or ExAC, present in 3.3%. Race, histologic subtype, and disease site were not predictive of mutation frequency. Patients with a BRCA2 mutation from the GOG trials had longer progression-free survival (hazard ratio [HR], 0.60; 95% CI, 0.45-0.79; P < .001) and overall survival (HR, 0.39; 95% CI, 0.25-0.60; P < .001) compared with those without mutations.

**Conclusions and Relevance** Of 1915 patients with OC, 347 (18%) carried pathogenic germline mutations in genes associated with OC risk. PALB2 and BARD1 are suspected OC genes and together with established OC genes (BRCA1, BRCA2, BRIP1, RAD51C, RAD51D, MSH2, MLH1, PMS2, and MSH6) bring the total number of genes suspected to cause hereditary OC to 11.


Background: Several studies have suggested that the ovarian cancer risk reductions associated with parity and oral contraceptive use are weaker in postmenopausal than premenopausal women; yet little is known about the persistence of these reductions as women age. This question gains importance with the increasing numbers of older women in the
were assessed by analyses after extended follow-up of the Women's Health Initiative (WHI) randomized clinical trial incidence, specific endometrial cancer histologies, and endometrial cancer mortality remains unsettled. These issues.

Methods evaluating continuous combined estrogen plus progestin use.

Results and internationally was reviewed, and specifically included original research and review articles.

Impact: This information, if duplicated in other studies, will be useful to preventive counseling and risk prediction, particularly for women at increased ovarian cancer risk due to a personal history of breast cancer or a family history of ovarian cancer.

March 2016
Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. RT Chlebowski, GL Anderson, GE Sarto, R Haque, CD Runowicz, AK Aragaki, CA Thomson, BV Howard, J Wactawski-Wende, C Chen, TE Rohan, MS Simon, SD Reed,JE Manson. JNCI J Natl Cancer Inst (2016) 108 (3): djv350 doi: 10.1093/jnci/djv350 full Background: While progestin addition to estrogen mitigates endometrial cancer risk, the magnitude of the effect on incidence, specific endometrial cancer histologies, and endometrial cancer mortality remains unsettled. These issues were assessed by analyses after extended follow-up of the Women's Health Initiative (WHI) randomized clinical trial evaluating continuous combined estrogen plus progestin use.

Methods: The WHI enrolled 16 608 postmenopausal women into a randomly assigned, double-blind, placebo-controlled trial. Women age 50 to 79 years with intact uteri with normal endometrial biopsy at entry were randomly assigned to once-daily 0.625mg conjugated equine estrogen plus 2.5mg medroxyprogesterone acetate (n = 8506) as a single pill or matching placebo (n = 8102). Follow-up beyond the original trial completion date required reconsent, obtained from 12 788 (83%) of surviving participants. Analyses were by intent-to-treat. All statistical tests were two-sided.

Results: After 5.6 years' median intervention and 13 years' median cumulative follow-up, there were fewer endometrial cancers in the combined hormone therapy compared with the placebo group (66 vs 95 case patients, yearly incidence, 0.06% vs 0.10%; hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.48 to 0.89, P = .007). While there were somewhat fewer endometrial cancers during intervention (25 vs 30, respectively; HR = 0.77, 95% CI = 0.45 to 1.31), the difference became statistically significant postintervention (41 vs 65, respectively; HR = 0.59, 95% CI = 0.40 to 0.88, P = .008), but hazard ratios did not differ between phases (P difference = .46). There was a statistically nonsignificant reduction in deaths from endometrial cancer in the estrogen plus progestin group (5 vs 11 deaths, HR = 0.42, 95% CI = 0.15 to 1.22).

Conclusion: In postmenopausal women, continuous combined estrogen plus progestin decreases endometrial cancer incidence.


Purpose. The purpose of this article was to broadly review the most up-to-date information pertaining to the centralization of ovarian cancer care in the United States (US) and worldwide.

Methods. Much of the present literature pertaining to disparities in, and centralization of, ovarian cancer care in the US and internationally was reviewed, and specifically included original research and review articles.

Results. Data show improved optimal debulking rates, National Comprehensive Cancer Network (NCCN) guideline adherence, and overall survival rates in higher-volume, more specialized hospitals, and amongst higher-volume providers.

Conclusions. Patients with invasive epithelial ovarian cancer, especially those with higher stages (III and IV), are better served by centralized care in high-volume hospitals and by high-volume physicians, who adhere to NCCN guidelines wherever possible. More research is needed to determine the policy changes that can increase NCCN guideline adherence in low-volume hospitals and low provider caseload scenarios. Policy and future research should be aimed at increasing patient access, either directly or indirectly, to high-volume hospital and high-volume providers, especially amongst Medicare, lower socioeconomic status, and minority patients.
PPM1D Mosaic Truncating Variants in Ovarian Cancer Cases May Be Treatment-Related Somatic Mutations.  
http://jnci.oxfordjournals.org.ezproxy.uky.edu/content/108/3/djv347.full

Mosaic truncating mutations in the protein phosphatase, Mg2+/Mn2+-dependent, 1D (PPM1D) gene have recently been reported with a statistically significantly greater frequency in lymphocyte DNA from ovarian cancer case patients compared with unaffected control patients. Using massively parallel sequencing (MPS) we identified truncating PPM1D mutations in 12 of 3236 epithelial ovarian cancer (EOC) case patients (0.37%) but in only one of 3431 unaffected control patients (0.03%) (P = .001). All statistical tests were two-sided. A combination of Sanger sequencing, pyrosequencing, and MPS data suggested that 12 of the 13 mutations were mosaic. All mutations were identified in post-chemotherapy treatment blood samples from case patients (n = 1827) (average 1234 days post-treatment in carriers) rather than from cases collected pretreatment (less than 14 days after diagnosis, n = 1384) (P = .002). These data suggest that PPM1D variants in EOC cases are primarily somatic mosaic mutations caused by treatment and are not associated with germline predisposition to EOC.


Jonathan Ledermann and colleagues report the ICON-6 randomised trial findings for the tyrosine kinase inhibitor cediranib in relapsed platinum-resistant ovarian cancer. Cediranib offered the prospect of improved efficacy with tolerable side-effects, and ICON-6 was a pragmatic trial to provide real-world evidence of the effectiveness, safety, and acceptability of cediranib plus chemotherapy (either concurrent or concurrent plus maintenance as long as patients were deriving benefit), compared with chemotherapy plus placebo. ICON-6 found “meaningful improvement in progression free survival” 2 (hazard ratio 0·56, 95% CI 0·44–0·72) for concomitant plus maintenance cediranib compared with placebo, as well as significantly more diarrhoea, hypothyroidism, and voice changes. However, after unexpected and major design changes were enforced, we still await data for overall survival; the safety data are less informative than might be necessary, and there are no convincing data yet for patient acceptability and quality of life, which can be particularly relevant to inform trade-offs between improved efficacy and increased side-effects. These design changes should not have been necessary, and clinical trials should be better structured to make sure this does not recur. The original study design promised more reliable evidence, but instead of randomly assigning roughly 2000 participants, the study underwent a major revision with just 387 participants randomly assigned because the drug company involved (AstraZeneca) decided (on Sept 14, 2011) to cease commercial development of cediranib, owing to negative findings for overall survival in three pivotal phase 3 studies on different cancers. 3 4 5 With insufficient remaining drug stock and its short shelf life, as well as AstraZeneca being unwilling to manufacture additional supplies, a fundamental redesign (or complete abandonment) became necessary. The researchers, in partnership with the independent Data Monitoring Committee (IDMC), and the funders should be congratulated on having the vision and creativity to redesign the study, within the constraints of the remaining drug available. They redefined the primary outcome from overall survival to progression-free survival, focused on comparing concomitant plus maintenance cediranib with placebo, and reduced power from 90% to 80%, with overall survival, toxic effects, and quality of life becoming secondary outcomes. This change meant that a revised sample size of 440 patients (for those on cediranib, 20 mg after the initial 30 mg dose was dropped) was used. The study finally randomly assigned 486 patients, of whom 456 receiving the 20 mg dose were analysed. Designing and executing large multinational trials is challenging, with many stakeholders (patients, clinicians, funders,
regulators, ethics committee members, drug companies, health-care providers) to accommodate and many reasons for why a study might not be completed as planned (stopping early for safety, efficacy, or so-called futility reasons). Over the past few decades, statistical methods for sequential designs and Bayesian designs have more recently been a plethora of innovative adaptive designs, coupled with improved remits and increased experience within iDMCs, and funders looking for better and more efficient designs, have allowed clinical trialists to deliver more efficient and responsive clinical trials. So there are many legitimate reasons to redesign a trial because a stakeholder decides to cease manufacturing the relevant drug is not, in our view, a legitimate reason—from a scientific perspective insight is lost into that compound and mechanism of action, and we are letting down participants who agree to take part in research by allowing this to happen. When trials are redesigned midstream, there are ethical challenges in consenting future participants, and also potentially re-consenting those recruited under the original process of informed consent, to make sure the participants are properly aware of the reasons for the redesign and the scientific value of the new study. Here, the redesign was driven by the cessation of manufacture of the drug, but likewise a public funder might take part in by allowing this to happen. When trials are redesigned midstream, there are ethical challenges in consenting future participants, and also potentially re-consenting those recruited under the original process of informed consent, to make sure the participants are properly aware of the reasons for the redesign and the scientific value of the new study. Here, the redesign was driven by the cessation of manufacture of the drug, but likewise a public funder might withdraw support for a study midstream due to a change in policy or a redesign of presented evidence value for the health-care system. Often, it is just as valuable to know with good precision that an intervention doesn't work, particularly if it is expensive or associated with considerable side-effects.


Background Angiogenesis is a validated clinical target in advanced epithelial ovarian cancer. Cediranib is an oral antiangiogenic vascular endothelial growth factor receptor 1–3 inhibitor that has shown antitumour activity in recurrent ovarian cancer. We assessed efficacy and safety of cediranib in combination with platinum-based chemotherapy and as continued maintenance treatment in patients with first relapse of platinum-sensitive ovarian cancer.

Methods In this randomised, three-arm, double-blind, placebo-controlled phase 3 trial, we randomly assigned patients aged 18 years or older with relapsed platinum-sensitive ovarian cancer at 63 centres in Australia, Canada, New Zealand, Spain, and the UK. Participants received up to six cycles of platinum-based chemotherapy (once every 3 weeks) then entered a maintenance phase. Participants were randomly allocated (2:3:3), with five stratification factors and in alternating blocks, to receive placebo alongside chemotherapy and then placebo only maintenance (arm A; reference), cediranib 20 mg once-daily alongside chemotherapy then placebo only maintenance (arm B; concurrent), or cediranib 20 mg once-daily alongside chemotherapy then cediranib 20 mg once-daily maintenance (arm C; maintenance). Patients continued treatment to progression or excessive toxic effects. The primary efficacy endpoint was progression-free survival between arms A and C. Efficacy analysis was by intention to treat. Safety was assessed in all patients who received the allocated study drug. This trial is registered with ClinicalTrials.gov, number NCT00532194; the ISRCTN registry, number ISRCTN68510403; and ANZ Clinical Trials Registry, number ACTRN1261000016003.

Findings We randomly assigned 456 women between Nov 13, 2007, and Dec 23, 2011; results presented are for 456 patients randomly assigned subsequent to the 30mg safety phase. During a median of 19.5 months (IQR 14–26) follow-up, 113 (96%) of 118 women assigned to arm A and 141 (86%) of 164 assigned to arm C had disease progression. Median progression-free survival was 11.0 months (95% CI 10.4–11.7) in arm C and 8.7 months (7.7–9.4) in arm A (hazard ratio 0.56, 0.44–0.72, p<0.0001). 156 (90%) of 174 patients in arm B had disease progression, and median progression-free survival was 9.9 months (95% CI 9.4–10.5). Diarrhoea, neutropenia, hypertension, and voice changes were significantly more common, during chemotherapy with cediranib, and diarrhoea, hypothyroidism and voice changes were more common during maintenance. Poor compliance with cediranib was noted during maintenance treatment with toxic effects being the most common cause for discontinuation.

Interpretation Cediranib, when given orally with chemotherapy and continued as maintenance, yielded a meaningful in progression-free survival in women with recurrent platinum-sensitive ovarian cancer, albeit with added toxic effects. The positive results in ICON6 could provide women with a new therapeutic option for recurrent ovarian cancer. Assessment of the secondary endpoint of overall survival will need longer follow-up.


Can Talc Cause Cancer? A jury recently awarded $72 million in a talcum-powder–ovarian cancer case, but the data linking the hygiene product to disease risk are inconclusive. K Grens The Scientist March 2 http://www.the-scientist.com/?articles.view/articleNo/45493/title/Can-Talc-Cause-Cancer/ &utm_campaign=NEWSLETTER_TS_The-Scientist-Daily_2016&utm_source=hs_email&utm_medium=email&utm_content=26891653&_hsenc=p2ANqtz-
Last week, jurors in Missouri concluded that Johnson & Johnson bore some responsibility in the death of Jackie Fox, who died of ovarian cancer. Fox’s family was awarded $72 million in a case against the pharmaceutical behemoth because, the jurors said, Johnson & Johnson failed to disclose that its talc-based feminine hygiene powder carried an ovarian cancer risk. “The message that was spoken loud and clear came from the jury last week,” Ted Meadows, an attorney with Beasley Allen—the firm that represented Fox’s family—told The Scientist. “They’re telling J & J it’s time to either remove talc from the market or allow women to make an informed choice by putting a warning on the bottle.” Yet, according to the company, the jurors’ decision was not rooted in evidence. “The recent jury outcome goes against decades of sound science proving the safety of talc as a cosmetic ingredient in multiple products,” Johnson & Johnson said in a statement sent to The Scientist. The truth, it appears, lies somewhere in between. Epidemiologic studies have produced mixed results, though many have found a slight increase in risk for ovarian cancer—roughly 30 percent—among women who use talcum powder in their genital areas. But as far as experimental evidence showing talc can cause cancer, “those studies are definitely needed,” said Katie Terry, an epidemiologist at Harvard Medical School who conducted a recent study looking at talc use and ovarian cancer risk. Daniel Cramer, an epidemiologist at Brigham and Women’s Hospital, was among the first to publish results linking talc with ovarian cancer, finding a small increased risk among users. (Cramer is a paid consultant for plaintiff’s lawyers in talc-cancer litigation.) In 2000, for instance, he and his colleagues used data from the large Nurses’ Health Study and found a 40 percent increased risk for one type of ovarian cancer among women who used talc. The researchers saw no elevated risk for other types of ovarian cancer. Last year, a case-control study led by Cramer’s team observed a 33 percent increase in ovarian cancer risk among women who applied talc genitally. And in a case report of a woman with ovarian cancer who used talc for decades, Cramer found evidence of the mineral in her pelvic lymph nodes. “Juries are very persuaded by the forensic evidence,” he told The Scientist. “If you put up a picture of a lymphatic channel with a talc particle in it, that’s pretty convincing.” Joshua Muscat, a cancer epidemiologist at Penn State University, however, is not so convinced. (He is a paid consultant for defense attorneys in talc-cancer cases.) Case-control studies can suffer numerous limitations, he said, such as recall bias—women with cancer might recall a potentially hazardous exposure more readily—and challenges in determining exposure. A more robust epidemiological design is the cohort study that tracks participants over time to see who develops disease. In 2014, using data from the Women’s Health Initiative, researchers from the University of Massachusetts-Amherst and colleagues found no link between genital or diaphragm-based talc powder use and ovarian cancer. “Here’s a true objective measure: talc-dusted diaphragms,” said Muscat. “There’s no increased risk at all.” The study included only post-menopausal women, noted Terry, which could help explain the difference between the Women’s Health Initiative study and others, including her team’s own. In 2013, Terry and colleagues compiled data from eight case-control studies and found a 24 percent increased risk for epithelial ovarian cancer among women who used genital powders. From the questionnaires, the researchers could not definitively tell whether the products included talc. “The data is suggestive that genital powder does increase risk,” Terry told The Scientist. She added that because ovarian cancer is rare, a 24 percent increase will likely not have a huge impact on the population. “It’s not like everybody who uses genital powder will get cancer. But there are very few modifiable factors for ovarian cancer.” It’s not yet clear from published experimental data whether talc used in the genital area can indeed travel to the ovaries, increasing a woman’s cancer risk. “There is no known biological mechanism—even if you thought talc could enter the reproductive tract and make contact with the ovaries—by which it could cause cancer,” said Muscat. “There are so many issues with this that it’s not really considered credible.”

A 2013 report by a Cosmetic Ingredient Review panel examined available toxicity and exposure evidence from studies on animals, cells, and humans, declaring talc safe for use. As for migration of talc to the ovaries, the results were inconclusive. Some experiments found talc in the ovaries of rats administered talc into the vagina, but did not find the same in rabbits and monkeys. A study of human ovarian tumors found talc particles in 75 percent of the cases, while five of 12 examined cases of healthy ovarian tissue samples taken from women with breast cancer also detected talc. “There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others),” the panel concluded. However, one of the studies the report cites that exposed human cell lines to talc found that it “increased proliferation, induced neoplastic transformation and increased [reactive oxygen species] generation time-dependently in the ovarian cells” and suggested the compound “may contribute to ovarian neoplastic transformation.” The Cosmetic Ingredient Review, an independent team funded by the Personal Care Products Council, did not respond to a request for comment. Most health agencies have not declared talc a risk factor for ovarian cancer, save for the World Health Organization’s International Agency for Research on Cancer, which concluded in 2010 that “perineal use of talc-based body powder is possibly carcinogenic to humans.” Cramer said he suspects the mechanism behind the link his team has observed between genital talc use and ovarian cancer has to do with inflammation. “It will be nice if we can put together an animal experiment to prove it,” he said. He agreed definitive experimental data are lacking. But it’s clear from last week’s trial against Johnson & Johnson that such evidence isn’t necessary to convince jurors. Meanwhile, hundreds of cases are waiting to be heard, including two that Meadows will present in court next month.

See also:  
http://jnci.oxfordjournals.org/content/92/3/249.full  
http://europepmc.org/abstract/med/26689397  
http://jnci.oxfordjournals.org/content/92/3/249.full

Background Laparoscopy has acquired an increasing role in the management of ovarian cancer. Laparoscopic cytoreduction could represent a new front for selected patients after neoadjuvant chemotherapy (NACT).

Objective We sought to assess feasibility and early complication rate of minimally invasive (MI) interval debulking surgery (IDS) in stage III-IV epithelial ovarian cancer (EOC) patients after NACT.

Study Design This is a phase II multicentric study in advanced EOC cases with clinical complete response after NACT, according to Gynecologic Cancer Intergroup and Response Evaluation Criteria In Solid Tumors criteria. Institutional review board approval was obtained and all patients signed written informed consent to be included in the protocol. The study was registered in clinicaltrials.gov (NCT02324595) and was named “MISSION” trial. For patients meeting inclusion criteria, surgical procedures started with diagnostic laparoscopy to confirm preoperative findings and assess surgical complexity. MI-IDS included hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, peritoneectomy, and bowel resection. Pelvic and/or aortic lymphadenectomy was not considered as standard procedure in these cases. Intraoperative and postoperative outcomes, time to restart chemotherapy, survival rate, and quality of life data were registered.

Results From December 2013 through February 2015, of 184 advanced EOC patients considered eligible for IDS, 52 (28.2%) met inclusion criteria and were enrolled in the study. For 22 (12%) of them, standard laparotomic approach was preferred because of intraoperative surgeon evaluation. Thirty (16.3%) patients received the planned treatment of MI-IDS. Median age was 61 (range 39-81) years and median body mass index was 24 (range 20-31) kg/m2. Median numbers of NACT cycles was 4 (range 3-7). Median operative time was 285 (range 124-418) minutes and median estimated blood loss was 100 (range 50-200) mL. Surgical procedures included 28 (93.3%) hysterectomy and bilateral salpingo-oophorectomy, 29 (96.6%) omentectomy, 2 (6.6%) appendectomy, 11 (36.6%) regional peritoneectomy, and 1 (3.4%) bowel resection. A residual tumor of 0 cm was reached in 29 (96.6%) patients and 0.5 cm in only 1 (3.4%) case. The vast majority of patients were discharged on postoperative day 2 (range 2-3). No early postoperative complications were registered. Median time to restart chemotherapy was 20 (10-30) days and all patients successfully completed the cycles. Histological findings showed 3 (10%) complete response, 9 (30%) microscopic residual disease, and 18 (60%) evidence of macroscopic residual disease. With a median follow-up of 10.5 month, 5 peritoneal and 2 lymph nodal recurrences were observed. Psychometric test revealed moderate discomfort in the vast majority of patients (66.7%). All patients are still alive.

Conclusion Invasive-IDS in patients with clinically complete response to NACT seems to be feasible and safe in terms of perioperative outcomes, psycho-oncological impact, and survival rate. The equivalence between MI surgery and laparotomy needs to be confirmed with a longer follow-up and a larger number of patients.


Recent changes in cervical cancer screening and management guidelines reflect our evolving knowledge about cervical carcinogenesis. In the pursuit of precision, however, decision-making has become complicated. We provide an overview of cervical cancer screening with a focus on what clinicians can do to maximize screening benefits while minimizing screening harms. The approach relies on categorizing women at each step in the screening process by their estimated risk of high-grade precancerous lesions and cervical cancer. Current screening guidelines are designed to find a reasonable balance between benefits and harms by recommending less screening in most women. Current management guidelines are designed to assure consistent decisions regarding referral to colposcopy. After initial colposcopy, we outline three major management options based on risk assessment. For treatment, we recommend ablational procedures when appropriate because they are similarly effective, less costly, and potentially safer than excisional procedures. We advise caution in adopting new screening strategies until they demonstrate cost-effective patient-centered improvements compared with current strategies. Clinicians can maximize their effect on cervical cancer prevention by being attentive to guidelines, assuring that women have access to appropriate human papillomavirus vaccination and providing low-cost, high-quality screening and treatment.
February 2016

Background: The K3326X variant in BRCA2 (BRCA2*c.9976A>T; p.Lys3326*; rs11571833) has been found to be associated with small increased risks of breast cancer. However, it is not clear to what extent linkage disequilibrium with fully pathogenic mutations might account for this association. There is scant information about the effect of K3326X in other hormone-related cancers.

Methods: Using weighted logistic regression, we analyzed data from the large iCOGS study including 76 637 cancer case patients and 83 796 control patients to estimate odds ratios (ORw) and 95% confidence intervals (CIs) for K3326X variant carriers in relation to breast, ovarian, and prostate cancer risks, with weights defined as probability of not having a pathogenic BRCA2 variant. Using Cox proportional hazards modeling, we also examined the associations of K3326X with breast and ovarian cancer risks among 7183 BRCA1 variant carriers. All statistical tests were two-sided.

Results: The K3326X variant was associated with breast (ORw = 1.28, 95% CI = 1.17 to 1.40, P = 5.9x10-6) and invasive ovarian cancer (ORw = 1.26, 95% CI = 1.10 to 1.43, P = 3.8x10-3). These associations were stronger for serous ovarian cancer and for estrogen receptor–negative breast cancer (ORw = 1.46, 95% CI = 1.2 to 1.70, P = 3.4x10-5 and ORw = 1.50, 95% CI = 1.28 to 1.76, P = 4.1x10-5, respectively). For BRCA1 mutation carriers, there was a statistically significant inverse association of the K3326X variant with risk of ovarian cancer (HR = 0.43, 95% CI = 0.22 to 0.84, P = .013) but no association with breast cancer. No association with prostate cancer was observed.

Conclusions: Our study provides evidence that the K3326X variant is associated with risk of developing breast and ovarian cancers independent of other pathogenic variants in BRCA2. Further studies are needed to determine the biological mechanism of action responsible for these associations.

Predicting Low Accrual in the National Cancer Institute’s Cooperative Group Clinical Trials.

Background: The extent to which trial-level factors differentially influence accrual to trials has not been comprehensively studied. Our objective was to evaluate the empirical relationship and predictive properties of putative risk factors for low accrual in the National Cancer Institute’s (NCI’s) Cooperative Group Program, now the National Clinical Trials Network (NCTN).

Methods: Data from 787 phase II/III adult NCTN-sponsored trials launched between 2000 and 2011 were used to develop a logistic regression model to predict low accrual, defined as trials that closed with or were accruing at less than 50% of target; 46 trials opened between 2012 and 2013 were used for prospective validation. Candidate predictors were identified from a literature review and expert interviews; final predictors were selected using stepwise regression. Model performance was evaluated by calibration and discrimination via the area under the curve (AUC). All statistical tests were two-sided.

Results: Eighteen percent (n = 145) of NCTN-sponsored trials closed with low accrual or were accruing at less than 50% of target three years or more after initiation. A multivariable model of twelve trial-level risk factors had good calibration and discrimination for predicting trials with low accrual (AUC in trials launched 2000–2011 = 0.739, 95% confidence interval [CI] = 0.696 to 0.783; 2012–2013: AUC = 0.732, 95% CI = 0.547 to 0.917). Results were robust to different definitions of low accrual and predictor selection strategies.

Conclusions: We identified multiple characteristics of NCTN-sponsored trials associated with low accrual, several of which have not been previously empirically described, and developed a prediction model that can provide a useful estimate of accrual risk based on these factors. Future work should assess the role of such prediction tools in trial design and prioritization decisions.
The American Cancer Society (ACS) breast cancer screening guidelines now recommend that women at average risk of developing breast cancer begin screening with mammography at age 45 years instead of 40, as recommended in the 2003 guidelines, and switch to biannual mammograms after age 55. Those modifications are the result of a rigorous review process aimed at weighing benefits and harms, with the most notable one being overdiagnosis, or detecting and treating a cancer that probably would not have presented a serious health risk to a woman during her lifetime.

The guidelines, published in October (JAMA 2015;314:1599–614; doi:10.1001/jama.2015.12783), were developed using an evidence-based review process that the Institute of Medicine recommended. That review process involved analysis of randomized trials, observational studies, and modeling/simulation studies with the ability to generate estimates of long-term outcomes. “These are ambitious guidelines,” said Richard C. Wender, M.D., chief cancer control officer at ACS. “They are more nuanced than our previous guidelines, which make them a challenge to understand. But they provide some important new data that can guide decision-making.” Yet these changes have raised concerns. That’s especially true since ACS, the U.S. Preventive Services Task Force (USPSTF), the American College of Obstetricians and Gynecologists (ACOG), and the National Comprehensive Cancer Network (NCCN)—four organizations charged with making screening recommendations—now differ, with USPSTF recommending that women begin screening at age 50 years and ACOG and NCCN recommending 40 years as the starting age. “This message is very confusing,” said Elizabeth Morris, M.D., a radiologist at Memorial Sloan–Kettering Cancer Center in New York and president of the Society of Breast Imaging. “In the clinic, we see that mammography detects cancer and improves outcomes. We don’t want to see a successful recommendation—starting mammography at 40—taken away.” According to Wender, however, the purpose of the guidelines is to recommend the right ages and screening intervals that will give women the highest likelihood of benefiting from the procedure. The intent is to avoid overdiagnosis as well as “false positives,” which can lead to unnecessary biopsies that occur more in young women and those screened more often. “The cancer community has been cognizant of issues surrounding overdiagnosis for quite a while,” said Barnett S. Kramer, M.D., M.P.H., director of the division of cancer prevention at the National Cancer Institute. “Raising awareness of harms is not easy and doesn’t lend itself to soundbites.”

**Devil in the Details** The guidelines include a combination of “strong” and “qualified” recommendations, with only the new starting age of 45 years classified as strong. The option to start screening at age 40 years received a qualified recommendation, as did the recommendations for screening intervals. A third recommendation, stating that women in...
their 70s should continue screening as long as their overall health is good and they have a life expectancy of 10 years or longer, also was classified as qualified. The reasoning behind many of these changes lies in several decisions made about how the data were reviewed. The first was the extensive use of observational studies as opposed to randomized clinical trials. Even with the limitations of observational trials, ACS determined that those studies are more reliable than the somewhat outdated randomized clinical trials. The second was to base the guideline on 5-year intervals rather than the 10-year intervals its 2003 version used. Looking at the data through that lens, ACS found that the incidence of breast cancer is 10% for women aged 45–49 years and 12% for women aged 50–54 years, compared with 6% for women aged 40–45 years. The higher numbers for the two older age groups led to the change in starting age. But because these numbers show some benefit to starting screening at 40 years, that approach received a qualified recommendation.

“There is no perfect age to start screening,” Wender said. “We recognize that many women place a high value on even small opportunities to reduce their risk of dying of breast cancer. But we also wanted to give them the evidence so that they could make an informed decision with their doctors.” Kirsten Bibbins-Domingo, M.D., Ph.D., M.A.S., is the Lee Goldman, M.D., Endowed Chair in Medicine and professor of medicine and biostatistics at the University of California, San Francisco, School of Medicine and vice-chairperson of USPSTF. She said that the USPSTF recommendations were derived using a similar process. She noted that the job of both USPSTF and ACS is “to put the science out there so that women can make their own decisions based on their own assessment of the evidence.” To determine screening intervals, ACS commissioned the Breast Cancer Surveillance Consortium to examine the association of screening interval with tumor characteristics among women aged 40–85 years. After assessing 15,440 women diagnosed within 1 year of annual screening and 2 years of biannual screening, investigators found that, compared with annual screening, the proportion of stage IIB tumors or higher and larger than 15mm was greater for premenopausal women undergoing biannual screening than for postmenopausal women. Nancy L. Keating, M.D., M.P.H., professor of health care policy and medicine at Harvard Medical School in Boston and Lydia E. Pace, M.D., M.P.H., of Brigham and Women’s Hospital in Boston, wrote the editorial accompanying the ACS study. According to them, this finding contributed to the decision to give a qualified recommendation for annual screening for women aged 45–54 years and biannual screening for women aged 55 or more years (JAMA 2015;314:1569–71; doi:10.1001/jama.2015.13086). Another change is that ACS guidelines no longer recommend clinical breast examinations, largely because its analysis found little evidence showing the benefits of these exams. Wender further clarified the thinking behind this recommendation: “A program of screening should not rely on an annual breast exam but instead should focus on mammography.” Therese Bevers, M.D., is professor of clinical cancer prevention and director of the Cancer Prevention Center at the University of Texas M. D. Anderson Cancer Center in Houston, as well as chair of the NCCN guideline panels on breast cancer screening. She challenged this assertion, noting

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<th>Differences in Recommendations for Screening Mammography for Women With Average Breast Cancer Risk</th>
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<tr>
<td><strong>2015 American Cancer Society Guideline</strong></td>
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<td>Aged 40-44 years</td>
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<td>Option to begin annual screening</td>
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<td><strong>Aged 45-54 years</strong></td>
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<td>Annual screening</td>
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<td>Aged 55 years and older</td>
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<td>Screen every 2 y</td>
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<td>Option to screen annually</td>
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<td><strong>Aged 75 years and older</strong></td>
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<td><strong>No recommendation</strong></td>
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Discuss with your doctor the best screening approach for you.

The draft 2015 USPSTF recommendation is similar to the 2009 recommendation.
that no significant new data have emerged since ACS’s 2003 recommendation. “This decision gives women another reason to avoid annual checkups, which are important for keeping them healthy and in touch with their doctors,” she said.

**Working Toward a Consensus**

The controversy that these guidelines ignited and the varied recommendations among professional societies led ACOG to address this issue head-on. It has scheduled a 2-day conference for late January to develop a consensus on screening guidelines. All the key players have been invited, and ACS plans to attend, along with representatives from NCCN and other professional societies. USPSTF also hopes to attend, with the caveat that, as the government’s recommending organization, it may not sign consensus documents. Bevers agreed, adding that she believes that the guidelines can be made simpler. “Something along the lines of annual mammograms beginning at age 40 and continuing until it is no longer necessary,” she said. “We should point out the benefits and harms but frame them in a less paternalistic way.” Nonetheless, Kramer points out that this is a complicated issue, with a spectrum of opinions. “To that extent, confusion is warranted,” he said. “Each woman can look at a neutral presentation of benefits and harms and then apply her own values to her decision.”


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**Early and multiple origins of metastatic lineages within primary tumors.** Z-M Zhaoa, B Zhaob, Y Baic, A Iamarinoa, SG Gaffneya, J Schlessingerd, RP Liftonb, DL Rimmc, Jeffrey P. Townsendsd. PNAS vol. 113 no. 8 > Zi-Ming Zhao, 2140–2145, doi: 10.1073/pnas.1525677113 [http://www.pnas.org/content/113/8/2140.full](http://www.pnas.org/content/113/8/2140.full)

Many aspects of the evolutionary process of tumorigenesis that are fundamental to cancer biology and targeted treatment have been challenging to reveal, such as the divergence times and genetic clonality of metastatic lineages. To address these challenges, we performed tumor phylogenetics using molecular evolutionary models, reconstructed ancestral states of somatic mutations, and inferred cancer chronograms to yield three conclusions. First, in contrast to a linear model of cancer progression, metastases can originate from divergent lineages within primary tumors. Evolved genetic changes in cancer lineages likely affect only the proclivity toward metastasis. Single genetic changes are unlikely to be necessary or sufficient for metastasis. Second, metastatic lineages can arise early in tumor development, sometimes long before diagnosis. The early genetic divergence of some metastatic lineages directs attention toward research on driver genes that are mutated early in cancer evolution. Last, the temporal order of occurrence of driver mutations can be inferred from phylogenetic analysis of cancer chronograms, guiding development of targeted therapeutics effective against primary tumors and metastases.

**Significance**

The knowledge that cancer is an evolutionary process is old, but only recently can sequencing technology provide data for clinically relevant evolutionary analyses of cancer. Approaches developed for evolutionary biology can reveal the relationship among clonal lineages, the ancestral states of gene sequences, and the timing of evolutionary events. We performed whole exome sequencing of cancer tissues from multiple sites of dozens of subjects, demonstrating nonlinear
patterns of tumor progression and early origins of metastatic lineages and quantifying the times of occurrence of driver mutations. These findings direct research attention away from the search for genes that induce metastasis toward genes that are mutated early in tumorigenesis, providing therapeutic targets effective against both primary tumors and metastases.


**BACKGROUND** A dose-dense weekly schedule of paclitaxel (resulting in a greater frequency of drug delivery) plus carboplatin every 3 weeks or the addition of bevacizumab to paclitaxel and carboplatin administered every 3 weeks has shown efficacy in ovarian cancer. We proposed to determine whether dose-dense weekly paclitaxel and carboplatin would prolong progression-free survival as compared with paclitaxel and carboplatin administered every 3 weeks among patients receiving and those not receiving bevacizumab.

Full Text of Background...

**METHODS** We prospectively stratified patients according to whether they elected to receive bevacizumab and then randomly assigned them to receive either paclitaxel, administered intravenously at a dose of 175 mg per square meter of body-surface area every 3 weeks, plus carboplatin (dose equivalent to an area under the curve [AUC] of 6) for six cycles or paclitaxel, administered weekly at a dose of 80 mg per square meter, plus carboplatin (AUC, 6) for six cycles. The primary end point was progression-free survival.

Full Text of Methods...

**RESULTS** A total of 692 patients were enrolled, 84% of whom opted to receive bevacizumab. In the intention-to-treat analysis, weekly paclitaxel was not associated with longer progression-free survival than paclitaxel administered every 3 weeks (14.7 months and 14.0 months, respectively; hazard ratio for disease progression or death, 0.89; 95% confidence interval [CI], 0.74 to 1.06; P=0.18). Among patients who did not receive bevacizumab, weekly paclitaxel was associated with progression-free survival that was 3.9 months longer than that observed with paclitaxel administered every 3 weeks (14.2 vs. 10.3 months; hazard ratio, 0.62; 95% CI, 0.40 to 0.95; P=0.03). However, among patients who received bevacizumab, weekly paclitaxel did not significantly prolong progression-free survival, as compared with paclitaxel administered every 3 weeks (14.9 months and 14.7 months, respectively; hazard ratio, 0.99; 95% CI, 0.83 to 1.20; P=0.60). A test for interaction that assessed homogeneity of the treatment effect showed a significant difference between treatment with bevacizumab and without bevacizumab (P=0.047). Patients who received weekly paclitaxel had a higher rate of grade 3 or 4 anemia than did those who received paclitaxel every 3 weeks (36% vs. 16%), as well as a higher rate of grade 2 to 4 sensory neuropathy (26% vs. 18%); however, they had a lower rate of grade 3 or 4 neutropenia (72% vs. 83%).

**CONCLUSIONS** Overall, weekly paclitaxel, as compared with paclitaxel administered every 3 weeks, did not prolong progression-free survival among patients with ovarian cancer.


The article by Moss et al 1 in the September issue contains several statements that, in our opinion, require clarification and comment. First, the authors state that the dualistic theory of ovarian carcinogenesis proposed by Shih and Kurman 2 in 2004 supports the proposition that epithelial “ovarian” cancer is not one entity with several histological subtypes but a collection of different diseases arising from different cells of origin, which may not originate in the ovarian surface epithelium. They further state that “a core component of this model is that most high-grade serous carcinomas are primarily of tubal rather than ovarian origin.” As defined by the term dualistic, the theory of ovarian carcinogenesis mentioned just emphasized that ovarian carcinomas are pathogenically of 2 different types: type 1 (low-grade endometrioid, clear cell, mucinous, and low-grade serous) and type 2 (high-grade serous [HGSC], high-grade endometrioid, carcinosarcomas, and undifferentiated) tumors.2 It did not refer to them as “a collection of different diseases arising from different cells” of extraovarian origin. In our opinion, the fact that one tumor type (HGSC) accounts for more than two thirds of the cases does not justify classifying ovarian carcinomas into only 2 types, lumping together the other four (low-grade endometrioid, clear cell, mucinous, and low-grade serous carcinomas) as “type 1 carcinomas”. In fact, the latter tumors are clinically, morphologically, and molecularly distinct diseases that individually bear resemblance neither to HGSCs nor to each other.

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Thus, classifying ovarian carcinomas into just 2 types (“types 1 and 2”) is artificial and limits progress in understanding the biology or improving the management of the less common types of ovarian carcinomas. When preparing this, we were reminded of the words of the eminent Scandinavian investigators of earlier times Drs. Lars Santesson and Hans Ludwig Kottmeier who began an essay on the classification of ovarian tumors as follows: “Ovarian cancer is not an entity but a group of diseases. Studies of the results of treatment must be based on homogeneous groups of tumours and not on mixtures of histologically and biologically different tumour types”.

Just a few of the many differences between the entities in the grouping “type 1” carcinoma are the following: endometrioid and clear cell tumors have a very significant association with endometriosis, not seen, except rarely, with mucinous carcinomas and LGSCs. Additionally, endometrioid and clear cell carcinomas often have an origin in adenofibromas, also rarely seen with the other 2 tumor types. Mucinous tumors in an uncertain but definitely notable percentage of cases are likely of teratomatous origin, which is completely lacking for the other 3 tumor types. The differences under the microscope are so striking as to make any comments trite. Furthermore, the underlying molecular genetic abnormalities differ significantly. For example, both endometrioid and clear cell tumor frequently have the genetic alterations found in carcinomas of the uterine corpus, that is, ARID1A, PTEN, PIK3CA, CTNNB1 mutations and microsatellite instability. In contrast, mucinous carcinomas and LGSCs often have KRAS mutations and other abnormalities of the mitogen-activated protein kinase pathway.

In their cases, Moss et al encountered a difference in overall survival between the different histological subtypes when matched for stage. Stage 3 mucinous and clear cell ovarian carcinomas had a poorer outcome compared to both HGSC and LGSC. Such results fail to validate the ability of the dualistic theory for predicting tumor prognosis, that is, according to the theory, clear cell and mucinous carcinomas are classified as “type 1 tumors” and should be associated with a more favorable prognosis than that of HGSC.

On the other hand, the proposal of a dualistic model of ovarian carcinogenesis was unrelated with the putative tubal origin of HGSC. Indeed, the type 1/type 2 model 2 was proposed in 2004; 2 or 3 years before that, the tubal origin of HGSC was suggested by the Brigham and Women’s group 4,5 after the discovery by Piek et al 6 of what is now known as serious tubal intraepithelial carcinoma (STIC) in risk resected salpingo-oophorectomy specimens. Subsequently, the Baltimore group declared itself in favor of the tubal origin of all HGSCs, and data were incorporated into the prefabricated dualistic theory.7

Moss et al state that “the focus needs to be moved from the ovary to the tube when considering screening if an impact on mortality is the objective. In response to the tubal hypothesis, and the apparent inability of current screening regimens to reduce mortality, there is now extensive international support for prophylactic salpingectomy as a primary prevention strategy”. Even if prophylactic salpingectomy at the time of benign gynecological surgery was first enthusiastically adhered to by some oncological societies, it has been recently questioned in view of the probable ovarian/surface epithelial origin of HGSC in many cases.9

Approximately 5% to 10% of BRCA-positive asymptomatic women have early HGSC, and 80% of them are associated with STIC. As a result, speculation that “all” HGSCs originated in the fallopian tube followed. However, pathogenesis/origin of HGSC is more complex as indicated by the following:

1. Only 40% of advanced HGSCs show STIC.9
2. Only 8% of HGSCs with SET (solid, pseudoendometrioid, transitional) morphology 11 show STIC.
3. High-grade serous carcinomas with SET morphology tend to be BRCA positive, patients are younger, and outcome is better.11

Thus, it seems that HGSC (BRCA positive and BRCA negative) is not a homogeneous disease. Several variables, including age, histotype, STIC +/-, and patient outcome, allow segregation of 2 tumor groups: (a) younger BRCA-positive patients, without STIC and with favorable outcome; and (b) older BRCA-negative patients, with STIC, and with unfavorable prognosis.9 Therefore, recent studies suggest that HGSCs have multiple origins including ovarian surface, tubal, and pelvic peritoneum.

The authors concluded that “the implication of the dualistic model of ovarian carcinogenesis means that a large proportion of cases that have been traditionally known as ovarian cancers do not in fact arise from the ovary, and the entity known as primary peritoneal carcinoma is likely to be a description of the pattern of spread of metastatic disease rather than being a separate disease entity”.1 Besides the lack of relationship between the dualistic model and the putative tubal origin of HGSC, cases of HGSC with exclusively peritoneal involvement, in which both the ovaries and fallopian tubes are free of tumor, occur and, in such cases, a primary peritoneal origin is universally considered.12,13 A recent publication reported that patients with primary peritoneal HGSC with regional lymph node metastasis, who were staged as stage IIIC, had significantly better overall survival compared with patients with stage IIIC primary ovarian serous carcinoma with both peritoneal and regional lymph node metastases. Therefore, contrary to the suggestion of Moss et al, the primary site of origin of HGSC could potentially influence prognosis.14

We think that terms such as tubo-ovarian, müllerian, or pelvic serous carcinoma should not be recommended because they create confusion for patients, physicians, and medical investigators. In view of the rarity of HGSCs associated with tubal tumor masses, it is unlikely that all HGSCs originate in the fallopian tube. In contrast, ovarian involvement is the rule in almost all cases. The term HGSC of ovary should be kept until the different origins of ovarian tumors are better understood.

BACKGROUND Widespread disparities in care have been documented in women with gynecologic cancer in the United States. This study was designed to determine whether structural barriers to optimal care were present during the preoperative period for patients with gynecologic cancer.

METHODS A retrospective review was conducted for patients undergoing surgery for a gynecologic malignancy at a public hospital or a private hospital staffed by the same team of gynecologic oncologists between July 1, 2013 and July 1, 2014.

RESULTS Two hundred fifty-seven cases were included for analysis (public hospital, 69; private hospital, 188). Patients treated at the private hospital were older (58 vs 52 years; P = .004) and had similar medical comorbidities (median Charlson comorbidity index at both hospitals, 6) but required fewer hospital visits in preparation for surgery (2 vs 4; P < .001). Public hospital patients had a longer wait time from the diagnosis of disease to surgery (63 vs 34 days; P < .001).

According to a multiple linear regression model, the public hospital setting was associated with a longer interval from diagnosis to surgery with adjustments for the insurance status, age at diagnosis, cancer stage, and number of preoperative hospital visits (P < .001).

CONCLUSIONS Patients at the public hospital were subject to a greater number of preoperative visits and had to wait longer for surgery than patients at the private hospital. Attempts to reduce health care disparities should focus on improving efficiency in health care delivery systems once contact has been established.

It's Totally Tubular…Riding The New Wave of Ovarian Cancer Research. R Perets R Drapkin Cancer Res January 1, 2016 76:10-17; doi:10.1158/0008-5472.CAN-15-1382 http://cancerres.aacrjournals.org/content/76/1/10.full

Hereditary breast and ovarian cancer syndrome carries significant mortality for young women if effective preventive and screening measures are not taken. Preventive salpingo-oophorectomy is currently the only method known to reduce the risk of ovarian cancer-related death. Histopathological analyses of these surgical specimens indicate that a high proportion of ovarian cancers in women at high risk and in the general population arise from the fallopian tube. This paradigm shift concerning the cell of origin for the most common subtype of ovarian cancer, high-grade serous carcinoma, has sparked a major effort within the research community to develop new and robust model systems to study the fallopian tube epithelium as the cell of origin of “ovarian” cancer. In this review, evidence supporting the fallopian tube as the origin of ovarian cancer is presented as are novel experimental model systems for studying the fallopian tube epithelium in high-risk women as well as in the general population. This review also addresses the clinical implications of the newly proposed cell of origin, the clinical questions that arise, and novel strategies for ovarian cancer prevention.

Establishment and Characterization of an In Vitro Model of Ovarian Cancer Stem-like Cells with an Enhanced Proliferative Capacity


The establishment of cancer stem-like cell (CSC) culture systems may be instrumental in devising strategies to fight refractory cancers. Inhibition of the Rho kinase ROCK has been shown to favorably affect CSC spheroid cultures. In this study, we show how ROCK inhibition in human serous ovarian cancer (SOC) cells can help establish a CSC system, which illuminates cancer pathophysiology and its treatment in this setting. In the presence of a ROCK kinase inhibitor, spheroid cultures of SOC cells expressed characteristic CSC markers including ALDH1A1, CD133, and SOX2, along with differentiation and tumorigenic capabilities in mouse xenograft models of human SOC. High expression levels of ALDH, but not CD133, correlated with spheroid formation CSC marker expression and tumor forming capability. In clinical specimens of SOC, high levels of ALDH1A1 correlated with advanced stage and poor prognosis. Pharmacologic or genetic blockade of ALDH blocked cell proliferation and reduced expression of SOX2, the genetic ablation of which abolished spheroid formation, whereas SOX2 overexpression inhibited ALDH1A1 expression and blocked spheroid proliferation. Taken together, our findings illustrated a new method to culture human ovarian CSC, and they defined a reciprocal regulatory relationship between ALDH1A1 and SOX2, which impacts ovarian CSC proliferation and malignant progression.

Accumulated Metabolites of Hydroxybutyric Acid Serve as Diagnostic and Prognostic Biomarkers of Ovarian High-Grade Serous Carcinomas

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Ovarian cancer is a heterogeneous disease of low prevalence, but poor survival. Early diagnosis is critical for survival, but it is often challenging because the symptoms of ovarian cancer are subtle and become apparent only during advanced stages of the disease. Therefore, the identification of robust biomarkers of early disease is a clinical priority. Metabolomic profiling is an emerging diagnostic tool enabling the detection of biomarkers reflecting alterations in tumor metabolism, a hallmark of cancer. In this study, we performed metabolomic profiling of serum and tumor tissue from 158 patients with high-grade serous ovarian cancer (HGSOC) and 100 control patients with benign or non-neoplastic lesions. We report metabolites of hydroxybutyric acid (HBA) as novel diagnostic and prognostic biomarkers associated with tumor burden and patient survival. The accumulation of HBA metabolites caused by HGSOC was also associated with reduced expression of succinic semialdehyde dehydrogenase (encoded by ALDH5A1), and with the presence of an epithelial-to-mesenchymal transition gene signature, implying a role for these metabolic alterations in cancer cell migration and invasion. In conclusion, our findings represent the first comprehensive metabolomics analysis in HGSOC and propose a new set of metabolites as biomarkers of disease with diagnostic and prognostic capabilities.

For decades, the aim of surgical treatment of ovarian cancer was to achieve optimum debulking, originally defined as no residual or any tumour left of less than 1·6 cm, although this was recently redefined as no residual disease. 4 5 To achieve the latter, more extensive surgical excision, sometimes necessitating removal of liver metastases, the spleen, or diaphragmatic peritoneal stripping, is needed. This extensive excision is not universally practised, and arguably is partly a cause of the variability in reported trials. 1 6 Du Bois and colleagues 3 proposed that the high proportion of patients with complete tumour clearance meant that a cohort of patients, categorised in ICON7 as high-risk, were classed as low-risk in this study; hence the improved efficacy in the low-risk patients. This finding shows, for the first time—some might say at last—the effect of surgical intervention on ovarian cancer chemotherapy trials.

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Not all gynaecological oncologists have or were trained in extensive surgical approaches, but development of the necessary skills and improved resection rates is feasible. Equally, the patient must be fit enough to tolerate such surgery and, correctly, patients are carefully selected. But what are the selection criteria? If not uniform, patient selection becomes variable, affecting those not operated on and therefore excluded from pertinent trials. Evidence is accumulating that shows changing practice regarding use of primary surgery. Hence, has the time come to standardise both surgery and patient selection for surgery? This debate seems necessary. Recruiting centres will probably need to reveal not only their normal complete resection rates in operated patients, but also those patients they deemed unsuitable for primary surgery. Otherwise, the population recruited becomes more skewed than at present. Consensus regarding an acceptable level of achieving no macroscopic disease after primary surgery would seem warranted. Alternatively, stratification in clinical trials, based on macroscopic clearance, could be undertaken. Equally challenging is ensuring that trial findings are relevant to the care given to the wider population. But even with these obstacles, the time has come for the gynaecological oncology community to tackle these issues and produce solutions.

**Cervical cancer diagnosis and the US Affordable Care Act**

TK Burki. Lancet Oncology, The, 2016-01-01, Volume 17, Issue 1, Pages e10-e10. [https://www-clinicalkey-com.ezproxy.uky.edu/#!/content/journal/1-s2.0-S1470204515005628](https://www-clinicalkey-com.ezproxy.uky.edu/#!/content/journal/1-s2.0-S1470204515005628)

The initial introduction of the US Affordable Care Act in 2010 was followed by an increase in the proportion of young women diagnosed with early-stage cervical cancer, according to new research. On Sept 23, 2010, a provision in the Act known as Dependent Coverage Expansion, allowing children to remain on their parents’ insurance policy until the age of 26 years, went into effect. Investigators examined the records of 6417 women aged 21–34 years who were diagnosed with primary invasive cervical cancer from 2007–09 (n=3937) and from 2011–12 (n=2480). 2010 was excluded from the analysis to allow the new system to become established. Of the 650 women aged 21–25 years with cervical cancer, the proportion diagnosed with early-stage disease was 67.9% in 2009, 84.3% in 2011, and 72.3% in 2012. Compared with women aged 26–34 years, there was a net increase of 9.0 (95% CI 2.0–16.2) percentage points (p=0.01) for women aged 21–25 years between the period before and after Dependent Coverage Expansion was implemented. Furthermore, a net increase of 11.9 (95% CI 4.3–19.5) percentage points were noted in receipt of fertility-sparing treatments (p=0.002). Women who had private health insurance were more prone to be diagnosed at an early-stage of the disease compared with those who were uninsured or covered by Medicaid (a US Government programme for people with low-income). "Our data are cross-sectional, so we cannot say with certainty that the increases in early-stage diagnosis and fertility-sparing treatment were due to the expanded coverage provision", lead author Xuesong Han (American Cancer Society, Atlanta, GA, USA) told The Lancet Oncology. But she pointed out that the differences in cervical cancer diagnosis between women aged 21–25 years and aged 26–34 years does suggest an association. The decrease reported in 2012 could be a random fluctuation or be representative of the typical trajectory of a screening programme, whereby the second year yields fewer cases than the first year. The authors’ results do not surprise Joanna Cain (University of Massachusetts Medical Center, Worcester, MA, USA). "With increased access more women are getting screened and therefore detected earlier, and the barrier for going into screening is much lower", she explained. Han now plans to assess in more detail the effects of the roll-out of the Affordable Care Act.

**Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study**


**Background**

Cancer drugs challenge health-care systems because of their high prices. No cross-country price comparison of cancer drugs for a large number of countries has been published. We aimed to survey the prices of cancer drugs in high-income countries (Europe, Australia, and New Zealand).

**Methods**

Based on comparability in terms of the economic situation and of the pharmaceutical system, we surveyed official list prices per unit at ex-factory price level of 31 originator cancer drugs in 16 European countries, Australia, and New Zealand as of June, 2013. Drug price data for the European countries were provided by the Pharma Price Information (PPI) service; Australian and New Zealand drug price data were retrieved from the respective pharmaceutical schedules.

**Findings**

In Austria, Denmark, Finland, Germany, Italy, Norway, Sweden, and the UK, price information was available for all or all but one drug surveyed whereas the availability of price data was restricted for some drugs in other countries, especially in New Zealand and Portugal. The difference of a drug price between the highest priced country and the lowest priced country varied between 28% and 388%. A few drugs had lower outliers, especially Greek and UK prices, and upper outliers (particularly prices in Switzerland, Germany, and Sweden). Overall, Greek prices ranked at a low level, whereas Sweden, Switzerland, and Germany showed price data in similarly high ranges.

**Interpretation**

Our results showed variations in ex-factory prices of originator cancer drugs in the 18 surveyed countries. However, the surveyed prices do not include discounts negotiated by funding organisations because these discounts are confidential. Because pricing authorities can also only use these official undiscounted prices when they set prices through the common policy of external price referencing, they risk overpaying. Our findings provide an evidence base for policy makers to decide whether further policy measures related to drug prices are needed.

Background Angiogenesis is a target in the treatment of ovarian cancer. Nintedanib, an oral triple angiokinase inhibitor of VEGF receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor, has shown activity in phase 2 trials in this setting. We investigated the combination of nintedanib with standard carboplatin and paclitaxel chemotherapy in patients with newly diagnosed advanced ovarian cancer.

Methods In this double-blind phase 3 trial, chemotherapy-naive patients (aged 18 years or older) with International Federation of Gynecology and Obstetrics (FIGO) IIB–IV ovarian cancer and upfront debulking surgery were stratified by postoperative resection status, FIGO stage, and planned carboplatin dose. Patients were randomly assigned (2:1) via an interactive voice or web-based response system to receive six cycles of carboplatin (AUC 5 mg/mL per min or 6 mg/mL per min) and paclitaxel (175 mg/m^2 ) in addition to either 200 mg of nintedanib (nintedanib group) or placebo (placebo group) twice daily on days 2–21 of every 3-week cycle for up to 120 weeks. Patients, investigators, and independent radiological reviewers were masked to treatment allocation. The primary endpoint was investigator-assessed progression-free survival analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01015118.

Findings Between Dec 9, 2009, and July 27, 2011, 1503 patients were screened and 1366 randomly assigned by nine study groups in 22 countries: 911 to the nintedanib group and 455 to the placebo group. 486 (53%) of 911 patients in the nintedanib group experienced disease progression or death compared with 266 (58%) of 455 in the placebo group. Median progression-free survival was significantly longer in the nintedanib group than in the placebo group (17·2 months [95% CI 16·6–19·9] vs 16·6 months [13·9–19·1]; hazard ratio 0·84 [95% CI 0·72–0·98]; p=0·024). The most common adverse events were gastrointestinal (diarrhoea: nintedanib group 191 [21%] of 902 grade 3 and three [<1%] grade 4 vs placebo group nine [2%] of 450 grade 3 only) and haematological (neutropenia: nintedanib group 180 [20%] grade 3 and 200 (22%) grade 4 vs placebo group 90 [20%] grade 3 and 72 [16%] grade 4; thrombocytopenia: 105 [12%] and 55 [6%] vs 21 [5%] and eight [2%]; anaemia: 108 [12%] and 13 [1%] vs 26 [6%] and five [1%]). Serious adverse events were reported in 376 (42%) of 902 patients in the nintedanib group and 155 (34%) of 450 in the placebo group. 29 (3%) of 902 patients in the nintedanib group experienced serious adverse events associated with death compared with 16 (4%) of 450 in the placebo group, including 12 (1%) in the nintedanib group and six (1%) in the placebo group with a malignant neoplasm progression classified as an adverse event by the investigator. Drug-related adverse events leading to death occurred in three patients in the nintedanib group (one without diagnosis of cause; one due to non-drug-related sepsis associated with drug-related diarrhoea and renal failure; and one due to peritonitis) and in one patient in the placebo group (cause unknown).

Interpretation Nintedanib in combination with carboplatin and paclitaxel is an active first-line treatment that significantly increases progression-free survival for women with advanced ovarian cancer, but is associated with more gastrointestinal adverse events. Future studies should focus on improving patient selection and optimisation of tolerability.


This Visualizing Health Policy infographic charts recent trends in employer-sponsored health insurance premiums. Between 1999 and 2015, premiums increased by 203%, outpacing both inflation and workers’ earnings. However, growth of premiums for family coverage slowed toward the end of that time period, from an average of 11% per year between 1999 and 2005 to 5% per year between 2005 and 2015. Between 2014 and 2015, the average premium for single and family coverage increased 4%, and over the past 5 years, deductibles increased faster than both premiums and wages. There is considerable variation in the premiums offered by different employers; 8% of covered workers are enrolled in a family plan worth more than $24,000, and 4% are in plans worth less than $10,000 annually. More than half of large employers conducted an analysis to determine whether they offered insurance plans that would be subject to the excise tax on high-cost employer-sponsored health coverage slated to take effect in 2018.
**Recent Trends in Employer-Sponsored Health Insurance Premiums**

### Average Annual Premium Increases for Family Coverage, 1999–2015
- **1999 to 2005:** 11%
- **2005 to 2010:** 5%
- **2010 to 2015:** 5%

### Average Premiums Increased by 4% Between 2014 and 2015
- **Employer Contribution:** $16,834
- **Worker Contribution:** $12,011
- **Total:** $28,845

### Increases in Premiums Between 1999 and 2015 Have Outpaced Inflation and Workers’ Earnings
- **Cumulative Increase**
  - Workers’ Contribution to Family Premiums
  - Health Insurance Premiums for Family Coverage
  - Workers’ Earnings
  - Overall Inflation

### Over the Past 5 Years, Deductibles Have Risen Much Faster Than Premiums and Wages
- **Cumulative Increase**
  - Single Coverage Deductibles
  - Single Coverage Premiums
  - Workers’ Earnings

### Distribution of Annual Premiums for Workers With Family Coverage, 2015
- **Percentage of Covered Workers**
  - Average Annual Premium $17,845
  - Distribution:
    - < $10,000: 4%
    - $10,000 to $11,999: 6%
    - $12,000 to $13,999: 12%
    - $14,000 to $15,999: 16%
    - $16,000 to $17,999: 19%
    - $18,000 to $19,999: 18%
    - $20,000 to $21,999: 12%
    - $22,000 to $23,999: 7%
  - Premiums above $24,000: 8%

### Many Employers Took Action in 2015 to Address Anticipated Excise Tax on High-Cost Plans
- Small Employers (3–199 Workers)
- Large Employers (≥200 Workers)

**Authors:** Michelle Long, MPH; Matthew Rae, MPH, MPA; Gary Claxton; Anne Jankiewicz, and David Rousseau, MPH, for the Kaiser Family Foundation


Background Accurate methods to preoperatively characterize adnexal tumors are pivotal for optimal patient management. A recent meta-analysis concluded that the International Ovarian Tumor Analysis (IOTA) algorithms such as the Simple Rules are the best approaches to preoperatively classify adnexal masses as benign or malignant.

Objective To develop and validate a model to predict the risk of malignancy in adnexal masses using the ultrasound features in the Simple Rules.

Study Design International cross-sectional cohort study involving 22 oncology centers, referral centers for ultrasonography, and general hospitals. We included consecutive patients with an adnexal tumor who underwent a standardized transvaginal ultrasound examination and were selected for surgery. Data on 5020 patients were recorded in three phases between 2002 and 2012. The five Simple Rules features indicative of a benign tumor (B-features) and the five features indicative of malignancy (M-features) are based on the presence of ascites, tumor morphology, and degree of vascularity at ultrasonography. Gold standard was the histopathologic diagnosis of the adnexal mass (pathologist blinded to ultrasound findings). Logistic regression analysis was used to estimate the risk of malignancy based on the ten ultrasound features and type of center. The diagnostic performance was evaluated by area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive and negative likelihood ratios (LR+, LR-), positive and negative predictive values (PPV, NPV) and calibration curves.

Results Data on 4848 patients were analyzed. The malignancy rate was 43% (1402/3263) in oncology centers and 17% (263/1585) in other centers. The AUC on validation data was very similar in oncology centers (0.917, 95% CI 0.901 to 0.931) and other centers (0.916, 95% CI 0.873 to 0.945). Risk estimates showed good calibration. 23% of patients in the validation data set had a very low estimated risk (<1%), 48% had a high estimated risk (≥30%). For the 1% risk cutoff, sensitivity was 99.7%, specificity 33.7%, LR+ 1.5, LR- 0.010, PPV 44.8% and NPV 98.9%. For the 30% risk cutoff, sensitivity was 89.0%, specificity 84.7%, LR+ 5.8, LR- 0.13, PPV 75.4% and NPV 93.9%.

Conclusion Quantification of the risk of malignancy based on the Simple Rules has good diagnostic performance both in oncology centers and other centers. A simple classification based on these risk estimates may form the basis of a clinical management system. Patients with a high risk may benefit from surgery by a gynecological oncologist, while patients with a lower risk may be managed locally.

Letter to the Editor on “Should All Cases of High-Grade Serous Ovarian, Tubal, and Primary Peritoneal Carcinomas Be Reclassified as Tubo-Ovarian Serous Carcinoma?” Int J Gynecol Cancer 2015;25: 1201–1207


The article by Moss et al 1 in the September issue contains several statements that, in our opinion, require clarification and comment. First, the authors state that the dualistic theory of ovarian carcinogenesis proposed by Shih and Kurman 2 in 2004 supports the proposition that epithelial “ovarian” cancer is not one entity with several histological subtypes but a collection of different diseases arising from different cells of origin, which may not originate in the ovarian surface epithelium. They further state that “a core component of this model is that most high-grade serous carcinomas are primarily of tubal rather than ovarian origin.”

As defined by the term dualistic, the theory of ovarian carcinogenesis mentioned just emphasized that ovarian carcinomas are pathogenically of 2 different types: type 1 (low-grade endometrioid, clear cell, mucinous, and low-grade serous) and type 2 (high-grade serous [HGSC], high-grade endometrioid, carcinosarcomas, and undifferentiated) tumors.2 It did not refer to them as “a collection of different diseases arising from different cells” of extraovarian origin.

In our opinion, the fact that one tumor type (HGSC) accounts for more than two thirds of the cases does not justify classifying ovarian carcinomas into only 2 types, lumping together the other four (low-grade endometrioid, clear cell, mucinous, and low-grade serous carcinomas) as “type 1 carcinomas”. In fact, the latter tumors are clinically, morphologically, and molecularly distinct diseases that individually bear resemblance neither to HGSCs nor to each other. Thus, classifying ovarian carcinomas into just 2 types (“types 1 and 2”) is artificial and limits progress in understanding the biology or improving the management of the less common types of ovarian carcinomas. When preparing this, we were reminded of the words of the eminent Scandinavian investigators of earlier times Drs. Lars Santesson and Hans Ludwig Kottmeier who began an essay on the classification of ovarian tumors as follows: “Ovarian cancer is not an entity but a
group of diseases. Studies of the results of treatment must be based on homogeneous groups of tumours and not on mixtures of histologically and biologically different tumour types”.3 Just a few of the many differences between the entities in the grouping “type 1” carcinoma are the following: endometrioid and clear cell tumours have a very significant association with endometriosis, not seen, except rarely, with mucinous carcinomas and LGSCs. Additionally, endometrioid and clear cell carcinomas often have an origin in adenofibromas, also rarely seen with the other 2 tumour types. Mucinous tumors in an uncertain but definitely notable percentage of cases are likely of teratomatous origin, which is completely lacking for the other 3 tumour types. The differences under the microscope are so striking as to make any comments trite. Furthermore, the underlying molecular genetic abnormalities differ significantly. For example, both endometrioid and clear cell tumour frequently have the genetic alterations found in carcinomas of the uterine corpus, that is, ARID1A, PTEN, PIK3CA, CTNNB1 mutations and microsatellite instability. In contrast, mucinous carcinomas and LGSCs often have KRAS mutations and other abnormalities of the mitogen-activated protein kinase pathway. In their cases, Moss et al encountered a difference in overall survival between the different histological subtypes when matched for stage. Stage 3 mucinous and clear cell ovarian carcinomas had a poorer outcome compared to both HGSC and LGSC.1 Such results fail to validate the ability of the dualistic theory for predicting tumor prognosis, that is, according to the theory, clear cell and mucinous carcinomas are classified as “type 1 tumors” and should be associated with a more favorable prognosis than that of HGSC. On the other hand, the proposal of a dualistic model of ovarian carcinogenesis was unrelated with the putative tubal origin of HGSC. Indeed, the type 1/type 2 model was proposed in 2004; 2 or 3 years before that, the tubal origin of HGSC was suggested by the Brigham and Women’s group 4,5 after the discovery by Piek et al of what is now known as serous tubal intraepithelial carcinoma (STIC) in risk resected salpingo-oophorectomy specimens. Subsequently, the Baltimore group declared itself in favor of the tubal origin of all HGSCs, and data were incorporated into the prefabricated dualistic theory.7 Moss et al state that “the focus needs to be moved from the ovary to the tube when considering screening if an impact on mortality is the objective. In response to the tubal hypothesis, and the apparent inability of current screening regimens to reduce mortality, there is now extensive international support for prophylactic salpingectomy at the time of benign gynecological surgery as a primary prevention strategy”. Even if prophylactic salpingectomy at the time of benign gynecological surgery was first enthusiastically adhered to by some oncological societies,8 it has been recently questioned in view of the probable ovarian/surface epithelial origin of HGSC in many cases.9 Approximately 5% to 10% of BRCA-positive asymptomatic women have early HGSC, and 80% of them are associated with STIC.9,10 As a result, speculation that “all” HGSCs originated in the fallopian tube followed. However, pathogenesis/origin of HGSC is more complex as indicated by the following: 1. Only 40% of advanced HGSCs show STIC.9 2. Only 8% of HGSCs with SET (solid, pseudoendometrioid, transitional) morphology show STIC. 3. High-grade serous carcinomas with SET morphology tend to be BRCA positive, patients are younger, and outcome is better.11 Thus, it seems that HGSC (BRCA positive and BRCA negative) is not a homogeneous disease. Several variables, including age, histotype, STIC +/-, and patient outcome, allow segregation of 2 tumor groups: (a) younger BRCA-positive patients, without STIC and with favorable outcome; and (b) older BRCA-negative patients, with STIC, and with unfavorable prognosis.9 Therefore, recent studies suggest that HGSCs have multiple origins including ovarian surface, tubal, and pelvic peritoneum. The authors concluded that “the implication of the dualistic model of ovarian carcinogenesis means that a large proportion of cases that have been traditionally known as ovarian cancers do not in fact arise from the ovary, and the entity known as primary peritoneal carcinoma is likely to be a description of the pattern of spread of metastatic disease rather than being a separate disease entity”.1 Besides the lack of relationship between the dualistic model and the putative tubal origin of HGSC, cases of HGSC with exclusively peritoneal involvement, in which both the ovaries and fallopian tubes are free of tumor, occur and, in such cases, a primary peritoneal origin is universally considered.12,13 A recent publication reported that patients with primary peritoneal HGSC with regional lymph node metastasis, who were staged as stage IIIC, had significantly better overall survival compared with patients with stage IIIC primary ovarian serous carcinoma with both peritoneal and regional lymph node metastases. Therefore, contrary to the suggestion of Moss et al, the primary site of origin of HGSC could potentially influence prognosis.14 We think that terms such as tubo-ovarian, müllerian, or pelvic serous carcinoma should not be recommended because they create confusion for patients, physicians, and medical investigators. In view of the rarity of HGSCs associated with tubal tumor masses, it is unlikely that all HGSCs originate in the fallopian tube. In contrast, ovarian involvement is the rule in almost all cases. The term HGSC of ovary should be kept until the different origins of ovarian tumors are better understood.

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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).