New Insights Into the Pathogenesis of Ovarian Carcinoma

Time to Rethink Ovarian Cancer Screening

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Recent discoveries about the pathogenesis of ovarian cancer have suggested that it can no longer be thought of as a single entity, but that the histologically defined ovarian cancer subtypes are different diseases, with different precursor lesions and distinct biomarker expression profiles. Most serous carcinomas probably arise from the fallopian tube. Clear cell and endometrioid carcinomas are associated with endometriosis and likely originate from ectopic endometrium. The focus of large ovarian cancer screening trials has been detection of macroscopic ovarian abnormalities by ultrasonography and detection of serum biomarkers associated with the most common (serous) subtype of ovarian cancer. The only completed and phase three randomized controlled trial failed to achieve the objective of reducing ovarian cancer mortality and was not able to demonstrate a stage migration effect of the screening. Future screening strategies have to incorporate our growing understanding of each subtype of pelvic (ovarian or fallopian tube) cancer, its organ of origin, and disease-specific biomarkers. We review how our current understanding of pathogenesis should prompt a reexamination of data from ovarian cancer screening studies and discuss potential designs for future screening strategies.

(Obstet Gynecol 2012;120:935–40)
DOI: http://10.1097/AOG.0b013e318269b8b1

Ovarian cancer remains the eighth most common malignancy among women worldwide, with more than 200,000 cases diagnosed annually, resulting in more than 140,000 deaths.[1] Among developed countries, it is the sixth most common malignancy in both incidence and mortality, with more than 100,000 new cases and more than 60,000 deaths. The most important prognostic factor in patients with ovarian carcinoma is stage. Patients with low-stage (stage I–II) tumors have a favorable prognosis, whereas most patients with advanced-stage (stage III–IV) tumors will die of disease. This observation forms the basis for the premise that early detection through screening programs, identifying ovarian tumors when they are still confined to the ovary (ie, "early" stage disease), will result in better outcomes for women with ovarian cancer. However, it has become apparent that the distribution of ovarian carcinoma histotypes diagnosed at low stage is fundamentally different than that of tumors that present with advanced-stage disease.[2] This commentary examines those differences and the implications that this has for ovarian cancer screening.

Ovarian carcinomas are subclassified based on histotype, with serous, endometrioid, clear cell, and mucinous carcinomas accounting for 98% of cases. The serous subtype recently has been subdivided into high-grade serous carcinoma and low-grade serous carcinoma; these subtypes can be reproducibly diagnosed and differ with respect to genetic risk factors, pathogenesis, and prognosis, with progression-free survival rates of 45 months and 19.8 months for low-grade serous compared with high-grade serous carcinomas, respectively.[3] Recent literature indicates that the origins of some ovarian carcinoma histotypes may not be ovarian, and that unique genetic mutations are associated with each histotype, as outlined in Table 1.[4]

It has been proposed that the most lethal form of ovarian malignancy, high-grade serous carcinoma, originates in the distal fallopian tube in most cases. Multiple lines of evidence[5] support this view, including studies of incidentally detected carcinomas in women with BRCA mutations who undergo risk-

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/12

Table 1. Summary of the Proposed Origins and Underlying Genetic Defects of the Major Ovarian Cancer Histotypes

Histotype	Site of Origin	Genetic Associations
High-grade serous	Fallopian tube	*p53, BRCA1, BRCA2*
Low-grade serous	Cystadenoma or adenofibroma	*BRAF, Kras, PIK3CA, MSI*
Clear cell	Endometriosis	*ARID1a*
Endometrioid	Endometriosis	*ARID1a, b-catenin, PTEN, MSI*
Mucinous	Tubal–peritoneal junction	*Kras, HER2*

reducing bilateral salpingo-oophorectomy, in which a majority of unifocal in situ or precursor lesions involve the fallopian tube mucosa at the fimbriated end but not the ovary.[6–8] In situ and precursor fallopian tube lesions not associated with BRCA mutations also are regularly identified when thorough pathologic examination of the fallopian tubes is performed.[9] Serous tubal intraepithelial carcinomas are present in 35%–60% of high-grade serous carcinomas, and up to 50% of high-grade serous carcinomas display complete overgrowth of the fallopian tube ipsilateral to the dominant adnexal mass.[10,11] For these reasons, a fallopian tube origin can be argued for most cases of sporadic high-grade serous carcinoma. Clear cell and endometrioid cancers appear to arise from endometriosis, with recent data implicating *ARID1A* as a common tumor-suppressor gene among these subtypes.[11] Finally, the origin of mucinous carcinomas remains unclear, but there is preliminary evidence of its relation to the tubal–peritoneal junction.[12]

Stage at presentation differs dramatically between ovarian carcinoma histotypes. Most low-stage ovarian carcinomas are nonserous types, whereas the majority of advanced stage carcinomas (90% or more) are high-grade serous carcinomas.[13] In a case analysis of more than 600 women, those with serous ovarian carcinoma had diagnoses at a more advanced stage and with a considerably shorter duration of symptoms than women with nonserous carcinomas.[14] It is rare to detect a high-grade serous carcinoma confined to the ovary (stage I). Of more than 2,000 cases of ovarian carcinoma, of which most were high-grade serous carcinoma (71%), in the Cheryl Brown Ovarian Cancer Outcomes unit[8] only 19 cases were apparent stage I high-grade serous carcinomas at diagnosis.[15] High-grade serous carcinomas are characterized by a very high mitotic rate and rapid growth. Although the tubal in situ lesions may be present for approximately 4 years, based on mathematical modeling,[16] once there is spread beyond the fallopian tube disease progression is rapid, with interval cases of advanced stage high-grade serous carcinoma detected in all the major screening studies. Screening thus must aim to detect the in situ lesion in the fallopian tube epithelium for this histotype.

Several screening modalities have been developed for cancer detection and prevention. The identification and removal of cancer precursor lesions have been used successfully to prevent invasive colon and cervical cancers. Serum biomarkers can be used to detect early-stage prostate cancer, and imaging techniques have been used to identify early-stage cancers of breast and lung.[17–20]

Screening strategies in ovarian cancer were based on the belief that ovarian cancer arose in the ovary and progressed in a step-wise fashion from early to advanced stages. Relying largely on serum markers and imaging, all of the major screening trials for ovarian cancer were completed or were actively accruing patients by the time new evidence about the biologic heterogeneity and etiology of ovarian cancer was emerging. Table 2 summarizes all the major screening trials conducted for the detection of ovarian cancer.

Early studies developed diagnostic protocols to expedite investigations based on symptoms, but symptoms at presentation usually indicate advanced disease.[25,26] In the most recent Diagnosing Ovarian Cancer Early study, patients who experienced early symptoms of ovarian cancer according to predefined criteria were enrolled to receive further work-up for ovarian cancer. The majority of high-grade serous carcinomas detected in this study were stage III or higher, with a stage distribution similar to that of patients within the population at large.[27] The Diagnosing Ovarian Cancer Early study is not a screening trial because its goal was to detect symptomatic early-stage disease.

CA 125, a serum biomarker associated with high-grade serous carcinoma, has been used in several prospective randomized screening strategies. This biomarker was combined with transvaginal ultrasonography in the Prostate, Lung, Colorectal, Ovarian Study and in a Japanese study, but the Prostate, Lung, Colorectal, Ovarian Study was not able to demonstrate an overall survival benefit and the Japanese study did not detect a higher incidence of

Table 2. Summary of the Major Ovarian Cancer Studies

Screening Trial	Type of Study	Population	Screening Modality	Dates	Results
UKCTOCS[21]	Randomized control trial	202,638 women	Annual Risk of Ovarian Cancer Algorithm (CA 125–based algorithm)	2001–2014	Ovarian cancer mortality, results TBA 2014
PLCO study[22]	Randomized control trial	78,216 women	Annual CA 125 for 6 y and annual transvaginal US for 4 y	1993–2010	No significant difference in ovarian cancer mortality
Japan Screening Study[23]	Randomized control trial	82,487 women	Annual CA 125 and transvaginal US	1985–2002	No significant difference in ovarian cancer incidence
Kentucky Ultrasound Screening Study[24]	Single–arm study	25,327 women	Annual transvaginal US	1987–2005	Describes ovarian cancer incidence and follow-up

UKCTOCS, United Kingdom Collaborative Trial of Ovarian Cancer Screening Study; TBA, to be announced; PLCO, Prostate, Lung, Colorectal, Ovarian; US, ultrasound.

ovarian cancers in asymptomatic women.[22,23] Annual CA 125 has been incorporated into a Risk of Ovarian Cancer Algorithm in the United Kingdom Collaborative Trial of Ovarian Cancer Screening Study, and the results are currently pending.[21] This study holds the best hope for identification of a screening strategy (ie, use of a biomarker with a risk of ovarian cancer algorithm) that can affect ovarian cancer mortality, and preliminary results suggest a positive predictive value of the screening test of approximately 25%.[21] Results are awaited with great anticipation, at least in part because if this large well-designed study fails, then we are left with no candidate approaches to screening for ovarian cancer that are promising enough to be ready for testing in a prospective randomized trial. At this time, there is no evidence that highly curable organ-restricted lesions are detectable by this technique.

Other screening strategies have considered imaging alone as in the single arm nonrandomized University of Kentucky Screening project using transvaginal ultrasonography.[24] This study showed that transvaginal ultrasonography followed by CA 125 identified 447 benign pelvic masses and 15 ovarian tumors of low malignant potential. Whereas 47 epithelial ovarian carcinomas were detected, there were 12 screen failures in which high-grade serous carcinomas were diagnosed within less than 12 months after a negative screen. Screening with transvaginal ultrasonography is based on the ability to detect a mass associated with the ovary. Given the nonovarian origins of ovarian cancer, detecting ovarian abnormalities indicates more advanced disease. In the Prostate, Lung, Colorectal, Ovarian Study, 33% of women with false-positive screening results underwent unnecessary surgery as part of the screening and work-up protocol. Furthermore, there was a 15% major complication rate in this group of women.[22] This reflects the lack of a predefined algorithm for follow-up of abnormal screen results such that primary care providers were left to independently make decisions concerning further evaluation and intervention. This is a significant weakness of this study; however, this may parallel real-world practice in which primary care physicians may be expected to make individualized decisions based on abnormal test results. Although direct visualization of the ovary may be more appropriate in detecting ovarian malignancies arising from the ovary (such as the non-high grade serous carcinoma histotypes), the data available from completed screening trials have not included adequate pathology detail and statistical power to confirm the benefit of screening for these less frequent, typically early-stage histotypes that, for the most part, are associated with a favorable prognosis.

Screening for a heterogeneous group of disease entities requires an understanding of each distinct etiology. Using a common screening modality is unlikely to be appropriate for all ovarian carcinoma histotypes. Targeting the ovaries as the primary site of malignancy is a flawed model when the majority of so-called ovarian cancers involve the ovaries secondarily. Also, using biomarkers that are only expressed in a subset of ovarian cancer types will undoubtedly bias the screening test and miss certain subtypes of ovarian cancers. For example, CA 125 is most sensitive as a biomarker for serous carcinomas and cannot be expected to detect nonserous cancers equally well.

Targeting the most common and aggressive histotype of ovarian malignancy, high-grade serous car-

cinoma, is necessary to significantly affect ovarian cancer mortality. Examining for high-grade serous carcinoma precursor lesions in the fallopian tube epithelium with imaging or direct visualization techniques is one potential approach. Similarly, use of genetic markers can be used to stratify risk, especially given the rapidly decreasing cost of DNA sequencing and genetic testing. Collection of fallopian tube secretions for analysis of specific biomarkers indicative of premalignancy or malignant transformation also may be explored. Proteins, or combinations of proteins, from either secretions or blood hold some promise. Deep sequencing technology looking for early and specific mutations associated with in situ or early-stage disease in DNA isolated from cervical os secretions warrants consideration. Likewise, pathogenic mutations in circulating DNA should be explored.

Screening for endometriosis-related carcinomas, of clear cell and endometrioid type, may be possible by looking for an ovarian mass, for example, by transvaginal ultrasonography. The histotype of detected cases in ongoing or recently completed studies using transvaginal ultrasonography should be examined carefully to determine whether there is the potential to detect these ovarian carcinoma subtypes with limited stage disease through screening. Because these histotypes are associated with a favorable prognosis, as noted previously, benefits of screening specifically for these histotypes may be outweighed by the risks of false-positive results or unnecessary interventions, even with a very good screening tool.

Future screening trials need to be randomized, need to have a well-defined protocol for evaluating and managing any identified screening abnormalities, and should incorporate centralized pathology review. The United Kingdom Collaborative Trial of Ovarian Cancer Screening study has most of these elements. It is a large, randomized study with a clear algorithm for both screening and managing positive screen results. However, a centralized pathology review is not part of the protocol and, because there may be significant histotype-specific differences in the efficacy of ovarian cancer screening, just as there are histotype-specific differences in response to treatment,[28,29] accurate pathologic assessment is essential. Analyzing data with respect to the different histotypes would be ideal; however, this may have limitations related to limited power for subset analysis.

Screening is not possible for all malignancies at present. There is great hope in United Kingdom Collaborative Trial of Ovarian Cancer Screening Study because it is a well-designed study using a defined algorithm to minimize unnecessary intervention; however, in the event that this is a negative study, we would be left with having to "start over" in the development of screening tools and attention would shift to prevention and treatment strategies as ways to decrease ovarian cancer mortality. Although the search should continue for an effective screening test for high-grade serous carcinoma in particular, there is still the possibility for prevention of high-grade serous carcinoma by removal of the fallopian tubes at the time of hysterectomy or tubal ligation. Hysterectomy is the second most common operation in the United States, with more than 600,000 procedures per year,[30] and tubal ligations are now performed 700,000 times per year.[31] By recommending salpingectomy at the time of these common procedures, we have the potential to significantly reduce the incidence of high-grade serous carcinoma. However, the advent of newer surgical procedures being performed in the office setting, for example, the hysteroscopic approach for tubal ligation (Essure Micro-Insert System) may reduce the opportunity to perform prophylactic salpingectomies. In Canada, the Society of Gynecologic Oncology has issued a position paper in 2011 recommending that bilateral salpingectomy at the time of hysterectomy should be discussed and considered for the prevention of ovarian cancer.[32]

For women who are BRCA mutation carriers who have a considerably higher risk of development of ovarian cancer, there is no evidence that screening reduces the incidence or mortality from ovarian cancer. The standard recommendation for these women is to offer risk-reducing surgery with bilateral salpingo-oophorectomy by age 40, or after child-bearing is complete.[33,34] Bilateral salpingo-oophorectomy is a highly effective intervention, reducing the risk of ovarian cancer by 80%–90%.[35] Because much of the evidence for the origin of high-grade serous carcinomas has come from women who are BRCA mutation carriers who have undergone risk-reducing bilateral salpingo-oophorectomy, it is tempting to speculate that simpler surgery such as bilateral salpingectomy, with or without subsequent oophorectomy (eg, at age 50), could be effective for cancer prevention. Salpingectomy would obviate symptoms associated with premature menopause, which have an effect on quality of life, but more importantly it would mitigate the cardiovascular risk associated with premenopausal oophorectomy.[36] Only approximately 60% of women with BRCA1 or BRCA2 mutations choose to undergo risk-reducing surgery,[37,38] and if salpingectomy is an effective surgical option, the proportion who choose risk-reducing surgery could be higher. However, the

health benefits of maintaining ovarian function with salpingectomy could be offset by an increased risk of breast cancer. A prospective study in France is currently accruing young women with BRCA mutations who are unwilling to undergo bilateral salpingo-oophorectomy but instead have laparoscopic salpingectomy (fimbriectomy) and are evaluated for short-term and long-term outcomes (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT01608074). Further observational studies are needed to compare outcomes of women undergoing salpingectomy or bilateral salpingo-oophorectomy, and those reluctant to have any risk-reducing surgery.

CONCLUSION

Previous ovarian cancer screening strategies have failed because it was not considered, or known, that "ovarian cancer" represents different diseases, distinguished by histotype, and that the origin of the most common histotype, high-grade serous carcinoma, is nonovarian in the majority of cases, with ovarian involvement as a manifestation of transcoelomic spread. Screening techniques for high-grade serous carcinoma based on detection of an ovarian mass inherently identify tumors with transcoelomic spread beyond the fallopian tube primary site, and serum biomarkers such as CA 125 have not been proven to be able to detect organ-confined disease in clinical trials. To be effective, future strategies in ovarian cancer screening will need to consider our current understanding of ovarian cancer pathogenesis and to specifically focus on the high-grade serous carcinoma subtype and the fallopian tube epithelium.

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