Ovarian Cancer Screening and Early Detection in the General Population

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Worldwide, the estimated annual incidence of ovarian cancer is 204,000, with 125,000 deaths. In developed countries, ovarian cancer remains the most lethal of all gynecologic malignancies. One of the reasons for the high fatality rate is that more than 70% of women with ovarian cancer are diagnosed with advanced disease. There is a close correlation between stage at presentation and survival; therefore, early detection of ovarian cancer represents the best hope for mortality reduction and long-term disease control. There is preliminary evidence that screening can improve survival, but the impact of screening on mortality from ovarian cancer is still unclear. The proteomic approach has yielded encouraging preliminary findings, but these findings are not mature enough for clinical use. At this time, clear recommendations cannot be made on the basis of the available data.
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Worldwide, the estimated annual incidence of ovarian cancer is 204,000 with 125,000 deaths.[1] In developed countries, ovarian cancer remains the most lethal of all gynecologic malignancies.[2] One of the reasons for the high fatality rate is that more than 70% of women with ovarian cancer are diagnosed with advanced disease. Five-year survival rates for women with advanced disease range from 20% to 30%; however, for women who are diagnosed when the disease is confined to the ovary, cure rates are approximately 70% to 90%.[3] Because there is a close correlation between stage at presentation (Table 1) and survival,

Table 1
Ovarian Cancer Staging by International Federation of Gynecology and Obstetrics Criteria (2002)

Stage I **Growth Limited to the Ovaries**
IA: Tumor limited to one ovary; capsule intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IB: Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
IC: Tumor limited to one or both ovaries with capsule rupture or tumor on ovarian surface; malignant cells in ascites or peritoneal washings
Stage II **Tumor Involves One or Both Ovaries With Pelvic Extensions**
IIA: Extension or implants on uterus or tube(s), or both; no malignant cells in ascites or peritoneal washings
IIB: Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings
IIC: Pelvic extension with malignant cells in ascites or peritoneal washings
Stage III **Tumor Involves One or Both Ovaries With Peritoneal Metastasis Outside the Pelvis or Retroperitoneal or Inguinal Node Metastasis**
IIIA: Microscopic peritoneal metastasis beyond pelvis
IIIB: Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
IIIC: Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension or regional lymph node metastasis, or both
Stage IV **Distant Metastasis (Excludes Peritoneal Metastasis) to Liver Parenchyma or Other Visceral Organs or a Malignant Pleural Effusion**

early detection of ovarian cancer represents the best hope for mortality reduction and long-term disease control.

The median age at presentation of ovarian cancer is 60 years, and the average lifetime risk for women in developed countries is about 1 in 70.[3] Most women diagnosed with ovarian cancer have the sporadic variety; however, a subset of ovarian cancer cases occur in a familiar fashion. For this subset, a strong family history of ovarian or breast cancer is the most important risk factor. Overall, hereditary predisposition accounts for at least 10% of all epithelial ovarian cancers. Mutations in the *BRCA* genes account for approximately 90% of these cases, with most of the remaining 10% attributable to Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).[4,5] The cumulative lifetime risk of ovarian cancer is 40% to 50% for *BRCA1* mutation carriers and 20% to 30% for *BRCA2* mutation carriers.[6,7] The cumulative risk of ovarian cancer in HNPCC families is more than 12%.[8] Nulliparity, early menarche, late menopause, and increasing age are also associated with increased risk, whereas oral contraceptive use, pregnancy, lactation, and tubal ligation are associated with reduced risk.[9,10]

The standard initial management of epithelial ovarian cancer consists of aggressive surgical cytoreduction, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, and platinum/taxane combination chemotherapy. Extensive and largely retrospective experience has shown that optimal surgical debulking with no residual tumor or residual tumor deposits that are less than 1 cm in size is associated with improved patient outcomes.[3] Despite advances in the treatment of ovarian cancer, effective screening, early detection, and cure remain elusive for most women.

The Challenge of Ovarian Cancer Screening

Evaluating potential screening tests for ovarian cancer has been extremely challenging for several reasons:

1. Given the prevalence of ovarian cancer (1 in 2500 in postmenopausal women) and the stringent requirements for an effective screening strategy, an effective ovarian cancer screening test would require a minimum positive predictive value (PPV) of 10%.[11] To achieve a PPV of 10% with a prevalence of 1 in 2500, a screening tool requires a sensitivity of 75% or greater for early-stage disease and a specificity of 99.6%. Moreover, as the diagnosis of ovarian cancer is generally made at surgery, a PPV of 10% would result in 10 surgeries for every 1 case of cancer detected.
2. The lack of established identifiable histologic precursor lesions or molecular events that precede malignant transformation.
3. The fact that neither the time required for development of invasive disease nor the interval between

stage I and stage III ovarian carcinomas is known.
4. Most biomarkers are developed and initially evaluated using samples from patients with clinically diagnosed and often advanced cancer—given the small number of true early-stage, high-grade carcinomas detected—often making it necessary to make inferences using cases of advanced disease rather than early-stage disease.[12]
5. The impact on ovarian cancer mortality can only be confirmed in a prospective, randomized, controlled trial, but the low prevalence in the general population means that very large prospective cohorts over a long time period are needed to evaluate the ability of a specific test.
6. Data have continued to accumulate that ovarian cancers detected early or those that are advanced at diagnosis, but where treatment results in prolonged survival, share a common underlying molecular biology, and that this underlying biology is different from that of the more common, virulent variety, usually diagnosed in late stages and associated with a worse outcome.[13,14] These findings suggest that even if current research efforts succeed in detecting early-stage ovarian cancer, the mortality from this disease may not be significantly affected because the cohort being detected and those responsible for the majority of ovarian cancer mortality may be two different entities.

Approaches to Screening for Epithelial Ovarian Cancer

Cancer Antigen 125

Cancer antigen 125 (CA-125) is a high molecular weight glycoprotein that is expressed by a large proportion of epithelial ovarian cancers. It is detected by the OC125 monoclonal antibody, which was first described by Bast and colleagues in 1981.[15] Since its discovery, CA-125 has become well established as a tumor marker for epithelial ovarian cancer. However, the sensitivity and specificity of CA-125 is known to be poor. It is only raised in approximately 50% of stage I epithelial ovarian cancers and in 75% to 90% of patients with advanced disease.[16-18] In addition, the specificity of the test is poor, and false-positive results have been noted in many medical disorders, both malignant[19] and benign.[20]

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Skates and colleagues[21] noted that a higher sensitivity was obtained for CA-125 if the rate of change in CA-125 serum levels in conjunction with age is used as predictor rather than a fixed cut-off value. In their study, patients with ovarian cancer showed progressive increases with time, whereas healthy women remained unchanged. Interpreting this additional information in serial CA-125 values using longitudinal statistical models retrospectively increased the sensitivity for detection of ovarian cancer from 70% to 86% while maintaining a high level of first-line specificity (98%). In this model in women without ovarian cancer, the expected CA-125 profile is flat at an individual's baseline level, whereas in women with undiagnosed ovarian cancer, the expected CA-125 profile is initially flat, but increases significantly, presumably because of tumor growth.[22]

Ultrasound

Ultrasound allows for detailed imaging of the ovaries and the detection of morphologic changes that may signify a developing malignancy. The transvaginal route is preferred because of the more detailed images obtained. Data acquired from ultrasound include details about the size of the ovaries, presence of abnormal ovarian lesions or other abnormal findings such as pelvic or abdominal fluid, and blood flow within the ovarian mass. All of these data have been evaluated as possible diagnostic variables for early detection of ovarian cancer. In addition, persistence of abnormalities on repeat scanning 4 to 6 weeks following initial detection helps reduce false-positive rates.[23,24]

Because most ovarian masses detected by ultrasound screening are benign,[25] it is essential that ultrasound images are interpreted in a manner that decreases observer variation and false-positive results. To decrease the number of false-positive results, many screening protocols use morphologic index–based criteria. These scoring scales include transvaginal ultrasound (TVUS) findings, such as ovarian volume, cyst wall structure, papillary vegetations, septation, and echogenicity for prediction of malignancy. There is no standardized index, with systems varying on the number and type of variables evaluated.[26-29] Sassone and

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colleagues[30] reported an index that scored four different morphologic characteristics of ovarian cyst architecture, including wall structure, cyst wall thickness, septation, and echogenicity. The scoring index had a sensitivity of 100% and a specificity of 83% in the differentiation of benign masses from malignant masses. In a different morphologic index,[31] which scored only three structural characteristics (ovarian volume, cyst wall, and septae), the sensitivity for ovarian cancer detection was 89%, and the specificity was 70%. Other early detection studies of ovarian cancer have coupled conventional ultrasound techniques with color Doppler imaging. However, in several reports, Doppler studies have not been shown to be superior to gray-scale imaging.[32,33]

Clinical trials involving ultrasound techniques for ovarian cancer screening have been undertaken since the 1980s. In one of the most extensive studies, van Nagell and colleagues[34] reported the results from more than 25,000 screened women with TVUS. Eligible women included all women aged 50 years or older and women aged 25 years or older with a documented family history of ovarian cancer in at least one primary or secondary relative. Abnormality criteria were simplistic and included an ovarian volume of more than 10 cm^3 in a postmenopausal woman, an ovarian volume of more than 20 cm^3 in a premenopausal woman, and any cystic ovarian lesion with an internal or papillary projection. Three hundred sixty-four women (1.4%) with a persisting ovarian tumor on TVUS underwent surgery. Thirty women were found to have invasive ovarian cancer, among whom 14 (47%) had stage I disease. Nine patients received the diagnosis of ovarian cancer within 12 months after a negative ultrasonographic assessment. The sensitivity of TVUS screening was 85%, and the specificity was 98.7%. The PPV of an abnormal screen was 14%. However, the fact that many of these patients were at high risk suggests that this PPV is higher than the value that would be expected in the general population.[35] In a different study, investigators from Hirosaki University (Hirosaki, Japan) reported on a large, population-based ovarian cancer screening program using TVUS. The number of women participating in the screening study was 183,043, and 324 women underwent surgery. Twenty-two patients were found to have ovarian cancer, and of these patients, 17 had primary invasive epithelial cancer, of which 12 patients were stage I. The authors concluded that TVUS screening was a viable method for the early detection of ovarian cancer.[36]

Even though these studies have shown somewhat favorable results, one of the important limitations of ultrasound has been the considerable variation among observers in interpreting and scoring ultrasonographic images. For example, Mol and colleagues[29] performed external validation of 21 different scoring systems and found that their performance was inferior to what was reported initially. Moreover, although ultrasound might provide excellent sensitivity in detecting ovarian lesions, it suffers from poor specificity and PPV.[25,37,38] Even in postmenopausal women there is a high rate of false-positive results given that there is a high prevalence of benign ovarian lesions in this group. This is exemplified by one study that demonstrated benign adnexal masses < 5 cm in 56% of postmenopausal women during autopsy; these women died of causes other than gynecologic or intraperitoneal cancer.[39] The detection of these benign tumors could lead to unnecessary surgery in healthy, asymptomatic women.

Combined Tests

Greater specificity can be achieved by a combination of CA-125 measurement and ultrasonography. Jacobs and colleagues[40,41] demonstrated that by using a screening strategy that involved a sequential approach with CA-125 as a primary test and pelvic ultrasonography as a secondary test, a high specificity and positive PPV (99.9% and 26.8%, respectively) were achieved. In a subsequent randomized, controlled trial of ovarian cancer screening using a screening strategy incorporating sequential CA-125 and ultrasonography, median survival was significantly increased in women with ovarian cancer in the screened group (72.9 months) when compared with the control group (41.8 months).[42] Other groups have tested variations of this multimodal strategy, some performing ultrasound first followed by serum CA-125 testing for women with abnormal ultrasound; others have proposed doing both tests concurrently. However, the main drawback of using a fixed cutoff of 30 U/mL for serum CA-125 in a screening model is its low sensitivity.[43]

Ovarian Screening Trials

Randomized, controlled trials have now been concluded in the general population to assess the impact of screening on ovarian cancer mortality. In the ovarian component of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial,[44] 78,237 healthy women aged between 55 and 74 years were randomly assigned to screening and control groups; 39,115 women were assigned to screening with annual serum CA-125 testing and TVUS. A CA-125 value at or above 35 U/mL or TVUS

with evidence of an abnormal ovarian volume or an ovarian cyst with papillary projections or solid components was considered a positive screen. In an initial report, among 28,506 women with results for both tests, 1703 had at least one abnormal test: 1338 had an abnormal TVUS, 399 had abnormal serum CA-125 levels, and only 34 had abnormalities in both. Among 570 women who underwent a surgical procedure, a total of 29 malignant neoplasms were identified; 9 were tumors of low malignant potential and 1 was an ovarian sexcord-stromal tumor (granulosa cell cancer). Of note, only 1 of the 19 invasive epithelial ovarian cancers was detected as stage I. The PPV was 3.7% for an abnormal CA-125 test, 1.0% for an abnormal TVUS, and 23.5% if both tests were abnormal. In a subsequent report after 4 years of screening, 3388 women had a positive result (either CA-125 or TVUS). Of these women, 1170 (34.5%) underwent surgery. Of the women who underwent surgery, 60 (5.1%) were found to have ovarian cancer; 72% of these tumors were stage III or IV. The screening effort did not change the expected stage distribution from that of a normal unscreened population. The PPV of a positive screening test was 1.0% to 1.3% during the 4 years of screening. Twenty-nine cases of ovarian cancer that were diagnosed during this study period were not detected by screening.

In the United Kingdom Collaborative Trial of Ovarian Cancer Screening,[45] 202,638 postmenopausal women aged between 50 and 74 years who were deemed to be at average risk for ovarian cancer were randomly assigned to no treatment (control group), TVUS screening alone (TVUS group), or a multimodal screening (MMS) group with annual measurement of CA-125 (evaluated over time on the basis of the risk of ovarian cancer algorithm) plus TVUS in cases in which the CA-125 level was elevated (MMS group). Women with abnormal results underwent further evaluation by a gynecologist and subsequently surgery in appropriate cases. In a preliminary report describing outcomes from the first 4 years, in the MMS group, 409 women were identified as high risk based on CA-125 levels, which decreased to 167 following TVUS and 97 following clinical assessment. Of these, 34 were found to have invasive ovarian cancer. In the TVUS group, 2785 were identified with abnormal ultrasound results; 1894 of these women required clinical assessment and 845 women underwent surgery—24 of whom were found to have invasive ovarian cancer. The sensitivity, specificity, and PPV for all primary ovarian and tubal cancers for the MMS group were 89.4, 99.8, and 43.3, respectively, versus 84.9, 98.2, and 5.5, respectively, in the TVUS group, with a significant difference in specificity between the groups. In the year after screening, ovarian cancer was diagnosed in 13 subjects with negative results on screening (8 in the TVUS group and 5 in the MMS group).

These two trials show conflicting preliminary findings. The UK trial's more favorable results may reflect differences in trial design. The UK trial defines an abnormal CA-125 level according to a risk of ovarian cancer algorithm to estimate ovarian cancer risk and used TVUS as a second-line test when CA-125 levels were abnormal, rather than as a primary screening modality. Although initial results of multimodal screening in the UK trial appear promising, definitive assessment awaits results from the effect on ovarian cancer mortality.

Novel Markers for Epithelial Ovarian Cancer

Efforts are diverted toward identifying new biomarkers that would improve sensitivity for the early detection of ovarian cancer. Researchers have explored different compartments, from the cancer cell itself to the immune response directed against the tumor, via the extracellular matrix, the vasculature, and the patient's fluids (blood, urine, ascites) using numerous approaches that span from transcripts to post-translational modifications.

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The most prominent of these new strategies involves the utilization of proteomics. Proteomics is the study of protein expression patterns, protein interactions, and protein pathways in the blood, individual organ systems, and tissue cells. Intracellular and extracellular protein interactions can result in modifications, degradations, and protein-coupling events that are reflected in the blood.[46]

Overall, proteomic studies have yielded numerous markers that unfortunately seem to perform, at best, similarly to CA-125.[47] It seems unlikely that a single marker for epithelial ovarian cancer will be clinically useful given the biologic heterogeneity of the disease.

At least 30 markers have so far been combined with CA-125 for this purpose. These studies, however, compared only two or three markers at a time and showed that sensitivity

has been improved by 5% to 15%, but specificity has inevitably been reduced. For example, in a study of 89 sera from patients with stage I ovarian cancer, use of three markers in combination (CA-125, OVX1, and macrophage colony-stimulating factor [M-CSF]) detected 84% of cancers, whereas CA-125 testing alone detected 69%. Specificity, however, declined from 99% to 84% with the combination.[48]

Visintin and colleagues validated a panel of six serum biomarkers (leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125) that showed differential expression in disease-free individuals and patients with ovarian cancer on microarray analysis.[49] This study serves as a follow-up to a previous study on a panel of four novel biomarkers (leptin, prolactin, osteopontin, and insulin-like growth factor II).[50] This analysis yielded a final model that combined observations from both sets to result in a sensitivity of 95.3%, specificity of 99.4%, PPV of 99.3%, and negative predictive value of 99.2%. However, this panel has received severe criticism by subsequent reports that have pointed out that the PPV estimate of 99.3% was based on a prevalence of ovarian cancer near 50%. The PPV was only 6.5% after recalculation on the basis of the true prevalence of ovarian cancer in the population.[51]

Recent reports have used surface-enhanced laser desorption and ionization (SELDI) to detect novel patterns of low molecular weight moieties in serum samples from patients with ovarian cancer. This proteomic technique has been reported to yield 100% sensitivity and 95% specificity with a PPV of 94%.[52] Although this is an encouraging preliminary study, few patients with early stage disease were included. In addition, other investigators have reported difficulty in reproducing the analysis from the primary data.[53]

Based on risk/benefit ratio, the various ovarian screening strategies discussed may be applicable in special female populations with ovarian cancer risk significantly higher than what is seen in the general population. Such select groups include women affected by *BRCA 1/2* mutations and Lynch syndrome. Further discussion of screening in this special population is beyond the scope of this review.

Conclusions

Decades of intense research have failed to produce a clinically applicable screening strategy for ovarian cancer in the general population. The proteomic approach has yielded encouraging preliminary findings that may later lead to a resolution of this important clinical problem. At this time, clear recommendations cannot be made on the basis of the available data. ■

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Main Points

- Hereditary predisposition accounts for at least 10% of all epithelial ovarian cancers. Mutations in the *BRCA* genes account for approximately 90% of these cases, with most of the remaining 10% attributable to Lynch syndrome (hereditary nonpolyposis colorectal cancer).
- Since its discovery, cancer antigen 125 (CA-125) has become well established as a tumor marker for epithelial ovarian cancer. However, the sensitivity and specificity of CA-125 is known to be poor. It is only raised in approximately 50% of stage I epithelial ovarian cancers and in 75% to 90% of patients with advanced disease.
- Because most ovarian masses detected by ultrasound screening are benign, it is essential that ultrasound images are interpreted in a manner that decreases observer variation and false-positive results. To decrease the number of false-positive results, many screening protocols use morphologic index–based criteria.
- Greater specificity can be achieved by a combination of CA-125 measurement and ultrasonography. Jacobs and colleagues demonstrated that, by using a screening strategy that involved a sequential approach with CA-125 as a primary test and pelvic ultrasonography as a secondary test, a high specificity and positive predictive value (99.9% and 26.8%, respectively) were achieved.
- Proteomic studies have yielded numerous markers that unfortunately seem to perform, at best, similarly to CA-125. It seems unlikely that a single marker for epithelial ovarian cancer will be clinically useful, given the biologic heterogeneity of the disease.

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