Introduction
In the United States in 2010, an estimated 21,880 women were diagnosed with ovarian cancer and 13,850 died of the disease. It is the most deadly of gynecologic cancers and responsible for the fifth highest mortality of all cancers in women.

Due to the nonspecific presenting symptoms, ovarian cancer is usually diagnosed in advanced stages. The primary treatment of ovarian cancer is tumor debulking and chemotherapy. For women with early-stage disease, the 5-year survival rate is 28% to 45%. Conversely, those diagnosed with early-stage ovarian cancer may achieve cure with adjuvant treatment. The 5-year survival rates for women diagnosed with early-stage disease range from 57% to 94%.

Controversy exists regarding the biology of early vs advanced disease: is it a continuum or does it represent two different biologic processes on a molecular level? Some believe that only indolent ovarian cancers are diagnosed in early stages. An understanding of the natural progression and origin of ovarian cancer is essential in discovering the most appropriate screening test but is beyond the scope of this article. For the purposes of this article, early ovarian cancer is assumed to progress to advanced ovarian cancer in a step-wise fashion.

Screening Tests
Preferably, a screening test would detect premalignant lesions before they became cancerous. The best screening...
test would detect premalignant conditions of the ovary, much as premalignant conditions of the cervix or colon are detected. Unlike cervical and colon cancer, the identity of a precursor lesion and how it develops into ovarian cancer is unknown. Without targeting precursor lesions, it is unlikely that a screening test would have a significant impact on cure. However, if able to detect early disease, screening may be able to improve interval survival. The value of using a screening test to merely extend survival rather than affect overall mortality is beyond the scope of this paper. For the purposes of this paper, a screening test would at minimum need to identify ovarian cancer in its early stages in order to have an impact in patient care.

To date, an effective screening tool for ovarian cancer has not been identified. A good screening test must satisfactorily address validity, reliability, yield, cost, acceptance, and follow-up services. Validity is determined by both sensitivity and specificity. A screening test needs to be positive for those with the disease (ie, sensitivity) and negative for those without the disease (ie, specificity). A screening test with poor sensitivity and specificity yields false-positive and false-negative results. In ovarian cancer, this translates to unnecessary surgery or inaccurate diagnosis.

In terms of ovarian cancer, an effective screening test must have a sensitivity greater than 75% and a specificity greater than 99.6% to attain a positive predictive value of 10%. A positive predictive value of 10% would limit unnecessary surgeries to 10 patients to identify 1 patient with cancer. The positive predictive value can be affected by prevalence of disease. The incidence of ovarian cancer in the general population is 17 per 100,000. Therefore, most women in the general population do not have ovarian cancer, and a positive result would likely be a false-positive outcome. With low incidence of disease, improving the accuracy of screening tests to provide an acceptable positive predictive value and even a negative predictive value is challenging.

Most studies aimed at finding a screening test focus on sensitivity, specificity, and positive predictive value. However, even valid tests must be reliable between observations and must yield the results necessary to change overall outcome. Although a test may identify ovarian cancer at an earlier stage, it may not be reproducible between institutions and may not alter overall survival. In addition, many of the proposed screening methods require new technology, which is expensive and not always readily available to the general public. Institutions may not have the personnel trained to administer or interpret the test. Therefore, the cost to the population, both monetarily and in the form of trained professionals, may delay an effective population screening program.

Subjective Symptoms
Symptoms preceding a diagnosis of ovarian cancer are neither specific nor sensitive. In 2006, Goff et al reported a case-control study including 149 women with ovarian cancer and 488 control patients. Through a questionnaire, they identified urinary urgency/frequency, pelvic/abdominal pain, increased abdominal size/bloating, and difficulty eating/feeling full as symptoms associated with cancer. They developed a symptom index that showed a sensitivity of 56.7% for early disease and 79.5% for advanced disease. Specificity was 90% for women older than 50 years of age and 86.7% for women younger than age 50.

In 2007, the Gynecologic Cancer Foundation, the American Cancer Society, and the Society of Gynecologic Oncologists followed with a consensus statement that “women experiencing bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary symptoms almost daily for more than a few weeks should see their doctor.” Although the symptom index allows for greater awareness, the index does not provide enough sensitivity and specificity for screening. Neither has the index been tested in a prospective manner. Studies since that time have combined the symptom index with other targets (eg, CA-125, HE4) in an attempt to improve positive predictive value, but the sensitivity and specificity remain too low for an adequate screening test.

Pelvic Examination
Pelvic examination is unlikely to discriminate an early or premalignant lesion from a normal ovary. The sensitivity in detecting a pelvic mass on pelvic examination is 45% and the specificity is 90%. In screening studies, a pelvic examination could distinguish a benign mass from a malignant mass with a pooled sensitivity of 58% and a specificity of 98%.

Tumor Markers
CA-125 is an epithelial marker derived from coelomic epithelium. It is elevated in 90% of advanced ovarian cancers and in 50% of early ovarian cancers. Any process that disrupts the epithelial lining of the peritoneum has the potential to raise the CA-125 level. Therefore, CA-125 can be elevated in many benign conditions including pregnancy, leiomyomata, ovarian cysts, endometriosis, appendicitis, and diverticulitis. CA-125 can also be elevated in other cancers such as uterine, colon, lung, or pancreas. It is neither sensitive nor specific enough to screen for early disease in ovarian cancer. Although one nested case-control study that included 37 women showed a sensitivity of 57% and specificity of 100% over 3 years, based on other data, the sensitivity of CA-125 for screening purposes is closer to 80%.

Therefore, CA-125 may help raise an index of suspicion when evaluating a pelvic mass, but it is not sufficiently sensitive or specific for effective screening.

Skates et al retrospectively evaluated CA-125 levels in a Swedish cohort. They applied linear regression to longitudinal CA-125 levels and hypothesized that changes in CA-125 over time may predict ovarian cancer. Their
algorithm for risk of ovarian cancer reached a specificity of 99.7% and a positive predictive value of 16%. The study was limited by sample size and retrospective design. However, it led to the development of the risk of ovarian cancer calculation later used in prospective trials discussed below.

**Imaging**

The most effective and least expensive imaging for ovaries is transvaginal ultrasound. Ultrasonography attempts to discriminate between benign and malignant adnexal masses by utilizing information on the morphology of wall structure, septations, echogenicity, and volume. Ultrasound has a pooled sensitivity of 82% to 91% and specificity of 68% to 81% at distinguishing benign from malignant masses. Doppler imaging utilized to discriminate between benign and malignant adnexal masses has a pooled sensitivity and specificity of 72% to 88% and 73% to 90%, respectively. Individually, sensitivities and specificities are as follows: resistive index, 72% and 90%; pulsatility index, 80% and 73%; maximum systolic velocity, 74% and 81%; and presence of vessels, 88% and 78%. Using morphology and Doppler imaging together resulted in a pooled sensitivity of 86% and a specificity of 91%. Although characteristics noted by ultrasound have been used to formulate a likely diagnosis of malignant vs benign masses, no characteristic has the sensitivity or the specificity necessary for ultrasound to be a reliable screening test. Like CA-125, these characteristics may raise an index of suspicion with an associated pelvic mass but are not sufficient for screening.

The Kentucky Ovarian Cancer Screening Project screened 14,469 asymptomatic women annually with ultrasound. An abnormal finding (abnormal volume for menopausal status or projections into a cystic tumor) resulted in repeat ultrasound and, if persistent, a subsequent CA-125. Using this paradigm, in 2000 they reported a sensitivity of 81%, a specificity of 98.9%, and a positive predictive value of 9.4%. Negative predictive value was 99.97%. In 2007 an update to this study was published that extended the screening to 25,327 women. Sensitivity reached 85%, specificity 98.7%, and positive predictive value 14.01%. Negative predictive value 99.9%.

A trial by the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) published in 2009 involving 202,638 patients showed that the use of ultrasound alone resulted in a sensitivity of 75% for invasive cancer and a specificity of 98.2% with a positive predictive value of 2.8%. However, UKCTOCS researchers found that when screening with CA-125 and using ultrasound as a second-line test for an abnormal CA-125 (determined according to a patented risk associated algorithm), sensitivity, specificity, and positive predictive value improved to 89.4%, 99.8%, and 43.3% overall, respectively, and 89.5%, 99.8%, and 35.1% for invasive cancers.

Menon et al also employed screening with CA-125 followed by the use of a risk of ovarian cancer algorithm. The algorithm determines an individual’s risk of ovarian cancer and was also used in the UKCTOCS trial. The algorithm is complex, and a discussion of its elements and calculations can be accessed through publications by Skates et al. If CA-125 results were abnormal with intermediate risk determined by the algorithm, the patient had repeat testing and subsequent ultrasound if indicated. If CA-125 results were abnormal with elevated risk determined by the algorithm, the patient underwent ultrasound. Among the 13,582 women screened, specificity was 99.8% and positive predictive value was 19%.

A comparable study — the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) — is in progress in the United States and has not yet reported long-term data. Preliminary results of 39,115 women randomized to receive screening for ovarian cancer showed a positive predictive value with CA-125 at 3.7%, with ultrasound at 1.0% and with both tests together a positive predictive value of 23.5%. Although the positive predictive value increased, if both ultrasound and CA-125 were required to be abnormal for screening in this trial, 20 of the 29 neoplasms (70%) and 12 of 20 invasive cancers (60%) would have been missed.

As technology improves, imaging may lead to earlier detection but is unlikely to have the specificity or sensitivity to identify early or premalignant lesions; if used alone, it is unlikely to be a good screening tool. Although recent studies are encouraging, they have yet to be validated. In addition, the use of ultrasound as a screening test is unlikely to be successful because ultrasound technique is highly dependent on the skill and training of both the ultrasonographer and the interpreting physician. As such, the use of ultrasound is unlikely to be consistently reproducible, accessible, or affordable for the general public and across institutions.

**Advancing Technologies**

Proteomic approaches include a test developed by OvaCheck (Correlogic Systems, Germantown, MD), which published its first results in 2002. Initial studies were enticingly optimistic, quoting a sensitivity of 100% and a specificity of 95% in distinguishing cancerous from normal ovarian tissue in 116 samples. However, the results were difficult to reproduce in independent evaluations of the data. In February 2004, the Society of Gynecologic Oncologists issued a statement that “more research is needed to validate the test’s effectiveness before offering it to the public.” OvaCheck has yet to be validated and is not commercially available.

The OvaSure Yale Ovarian Cancer Test (Laboratory Corporation of America, Burlington, NC) was recently introduced as a commercially available blood test. Data were initially presented in 2008. The initial study combined six biomarkers (leptin, prolactin, osteopon-
ovarian cancer), the final model was able to distinguish normal from cancerous tissue with 95.3% sensitivity, 99.4% specificity, and a positive predictive value of 99.3%. However, the OvaSure release to the market was considered premature, and it is currently unavailable. The US Food and Drug Administration was not satisfied with the validation of the testing and has asked for further evaluation.\(^3\) In July 2008, the Society of Gynecologic Oncologists stated that “it is our opinion that additional research is needed to validate the test’s effectiveness before offering it to women outside of the context of a research study.”\(^7\) One criticism of the study is that the positive predictive value was based on a prevalence of ovarian cancer of 50%.\(^3\) When calculating the positive predictive value using the prevalence of disease in the population, it decreases to 6.5%.\(^3\)

Additional serum markers are being researched. Both are moving to high throughput microarray assays resulting in vast numbers of data points. Bioinformatic analysis of such multiple point data sets is limited by statistical methods available to adequately evaluate the data with reproducibility and validity.\(^19,36\) However, with emerging technology and capabilities, this is likely a future direction for screening and individualizing diagnosis and treatment.

Additional serum markers are being researched. Perhaps in proper combination, markers may provide the needed specificity, sensitivity, and positive predictive value for effective screening, but this has not yet been determined.\(^6,8\) Although combining markers may increase the sensitivity, it may also decrease specificity.\(^8\) Markers that have been implicated include CA-72-4, macrophage colony-stimulating factor, monoclonal antibody OVX1, lyso phosphatidic acid, prostatin, osteopontin, inhibin, kallikrein, claudin 3, monoclonal antibody DF3, vascular endothelial growth factor, MUC1, CA-19-9, mesothelin, human epididymis protein 4, and interleukins.\(^3,6,8\) Additional targets continue to be identified as research enters high throughput modalities.\(^7\)

**High-Risk Populations**

Hereditary syndromes account for 10% of ovarian cancers.\(^3,38\) The risk of developing ovarian cancer is 39% to 46% for patients with BRCA1 mutations, 10% to 20% for those with BRCA2 mutations, and 9% to 12% for those with Lynch syndrome.\(^3,39,41\) Despite a higher prevalence of ovarian cancer among patients with these syndromes, no effective screening method is available.

There is no evidence that biomarkers such as CA-125, HE4, or mesothelin are more specific in high-risk populations.\(^42,43\) Although there may be utility in combining multiple markers in the future,\(^43\) no current combination of markers has been validated for screening purposes.

Annual screening with ultrasound and CA-125 has been unsuccessful in detecting early ovarian cancers in high-risk populations.\(^41,44\) In a retrospective audit of patients undergoing yearly surveillance with ultrasound and CA-125, Woodward et al\(^41\) found the sensitivity, specificity, and positive predictive value of screening in the high-risk cohort (N = 179) to be 50.0%, 82.9%, and 1.3%, respectively.\(^41\) Only one of four ovarian cancers in the cohort (N = 341) was discovered during routine surveillance. Furthermore, three of the four cancers were advanced. The authors concluded that annual screening is ineffective in high-risk populations.\(^41\)

A high-risk screening program in the Netherlands followed BRCA1 and BRCA2 patients biannually and other high-risk populations annually. Investigators noted a sensitivity of 40%, a specificity of 99%, and a positive predictive value of 40% combining CA-125 with transvaginal ultrasound.\(^45\) However, 80% of the patients diagnosed with cancer at the time of prophylactic salpingo-oophorectomy had negative screening prior to surgery.\(^45\) In addition, three of the four ovarian cancers detected during screening were identified in advanced stages, an endpoint unlikely to affect overall mortality.\(^45\)

Although there are no validated screening methods for patients at high risk of ovarian cancer, the National Comprehensive Cancer Network has offered expert opinion. Their guidelines suggest practitioners consider surveillance for high-risk patients with a pelvic examination, transvaginal ultrasound, and CA-125 every 6 months. Surveillance should begin at age 35 years or 5 to 10 years prior to the earliest age of diagnosis in the family.\(^37,46\) However, the guidelines stipulate that the effectiveness of this strategy is undetermined.\(^37,46\) The ability of ultrasound and CA-125 to decrease mortality associated with ovarian cancer in high-risk populations has yet to be proven.\(^37\)

**Conclusions**

At present, no validated testing modality is available with enough sensitivity, specificity, and positive predictive value to be used as a screening test for ovarian cancer. Currently, no organizations recommend screening in the general population.\(^3\) Despite developing technologies...
and some promising studies, it is unlikely that a screening test will be available in the near future. Even if one could achieve the necessary statistical criteria, developing an effective screening test for ovarian cancer will need to address many unresolved issues.

To date, we do not fully understand the progression of ovarian cancer from early to advanced disease. We do know that as the cancer presents on the surface of the ovary, peritoneal fluid circulates over the ovary, transporting cancer cells and depositing them throughout the abdominal cavity. This occurs on a microscopic level that is unlikely to be detected by imaging or laboratory values until the disease has significantly disseminated and progressed to advanced cancer. Until nanotechnology advances, screening tests employing current imaging techniques are unlikely to be sensitive enough to detect such microscopic changes.

Further, we have yet to identify a precursor lesion in ovarian cancer. Screening for precursor lesions offers the potential opportunity to impact mortality from ovarian cancer. If screening is limited to early diagnosis, it must achieve the necessary statistical criteria, developing an effective screening test for ovarian cancer. Aside from a clinical trial, routine screening will require training and costly investment that are essential to provide the necessary technology and personnel qualified to deliver reliable outcomes. Once a screening test has been validated sufficiently, it will still require a cost-benefit analysis.

To date, there is no effective screening method for ovarian cancer. Aside from a clinical trial, routine screening for ovarian cancer in the general public is not currently recommended. For patients at risk for ovarian cancer, biannual surveillance with ultrasound and CA-125 can be considered.

References


41. Woodward ER, Sleightholme HV, Considine AM, et al. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. BJOG. 2007;114(12):1500-1509.


