Screening for Ovarian Cancer: What We Know, What We Need to Know

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The majority of women with ovarian cancer present with advanced-stage disease. Women with early-stage ovarian cancer have a much better chance of achieving a cure than do women with late-stage disease. This

Introduction

Screening for certain cancers has been shown to increase disease-specific and overall survival, thus leading to recommendations that certain screening tests (eg, Pap smears, annual mammography for women over 50 years of age) be offered as standard care for the general population. When a screening test is being considered for use, the condition being screened for should meet the following criteria:

(1) The prevalence of the disease in the general population should be relatively high.
(2) The disease should cause substantial morbidity and mortality.
(3) Earlier diagnosis of the condition should result in an improved outcome.
(4) There should be an effective screening test for detection of the condition.

It is useful to apply these criteria to the issue of screening for ovarian cancer. More than 25,000 women are diagnosed with ovarian cancer annually in the United States and approximately 14,500 women die from the disease each year. Both the incidence and associated mortality of ovarian cancer appear to be increasing. In the general population, the lifetime risk of developing ovarian cancer is approximately 1.4%. However, among certain women, the risk is much higher. One of the strongest risk factors for developing the disease is having a close family member with ovarian cancer. The relative risk among women with a single first-degree relative with ovarian cancer is 3.1 (95% confidence interval: 2.6–3.7),[1] and if more than one relative has been affected, the relative risk is higher.[2]

Although shared exposures and sociocultural characteristics such as child-bearing choices may explain some of the increased risks within families, a genetic tendency to develop ovarian cancer is likely to be present in families with multiple cases of ovarian cancer. For example, women who are known to be carriers of germ-line mutations in the breast/ovarian cancer predisposition genes, BRCA1 or BRCA2, have a lifetime risk of developing ovarian cancer that is estimated to be between 16% and 65%.[3,4] It is likely that current ovarian cancer screening techniques may be most useful in this population of women in whom prevalence is relatively high.

Ovarian cancer clearly causes substantial morbidity and mortality, with 5-year survival averaging approximately 45%. The disease also meets the third screening criterion, since 5-year survival among women with stage I or stage II ovarian cancer is 80% to 90% vs 5% to 50% for women with stage III or IV. Nevertheless, screening efforts for the detection of ovarian cancer in the general population have, to date, been disappointing—the result of the lack of a highly effective screening test, and the low prevalence of the disease.

Evaluating Screening Tests

Sensitivity vs Specificity

The effectiveness of any screening test may be measured in terms of certain test parameters. Sensitivity refers to the ability of the test to detect the cancer. Specificity refers to the ability of the test to rule out cancer. Using the letter designations in Table 1, sensitivity is defined as the true-positive patients (a), divided by all the patients in the population who truly have cancer, ie, the true positives plus the false negatives (a + b). Specificity is defined as the true negatives (d) divided by all the patients who truly do not have cancer, ie, the true negatives plus the false positives (c +
There is a trade-off between sensitivity and specificity, such that no test possesses both 100% sensitivity and 100% specificity. Highly sensitive tests are unlikely to miss cancers, but many patients will undergo further testing or treatment for benign disease. Tests that are highly specific will give fewer false-positive results but will falsely reassure some patients that they are cancer-free. **Positive Predictive Value**

Equally important for evaluating the effectiveness of screening tests is the prevalence of the disease in the population to be screened; the positive predictive value (PPV) of a test incorporates this parameter. The importance of disease prevalence in determining the PPV can be seen in the equation for its calculation (where $S = $ sensitivity and $P = $ prevalence):

$$PPV = \frac{(S \times P)}{[(S \times P) + (1 - S)(1 - P)]}$$

Thus, the PPV value will vary among different screening populations, even when sensitivity and specificity are the same. For example, if an elevated serum CA-125 value has a sensitivity of approximately 80% for ovarian cancer and a specificity of 99% in the general population, with an ovarian cancer prevalence of 0.0003, its PPV is 2.3%. In a high-risk population with an ovarian cancer prevalence of 0.005, the PPV of an elevated CA-125 is 28.7%.

The low PPV in the general population raises concerns that screening the general population will generate many false-positive results that require surgical evaluation. For example, in the general population, 50 women would need to undergo laparoscopy/laparotomy to find one ovarian cancer. It has been suggested that a PPV of 10% is "reasonable" for an ovarian cancer screening strategy. Adopting a strategy with a PPV of 10% would mean that 10 women would undergo invasive surgery for each ovarian cancer found; i.e., in order for a test to have a PPV of 10% in the general population (prevalence of 0.0003, sensitivity of 83%), its specificity must be greater than 99.7%.

**Ovarian Cancer Screening Tests**

Ovarian cancer screening studies have been carried out in a variety of patient populations, utilizing one-time, serial, or single screening tests, or combinations thereof. However, many studies have been limited to postmenopausal women, in whom false-positive test results turn up less frequently (and in whom ovarian cancer incidence is higher) than in premenopausal women. Some studies have excluded women with strong family histories of ovarian cancer. Most studies have not had a no-screening control group and, therefore, could not assess the impact of screening on mortality.

**Serum CA-125 Levels**

Measurement of serum CA-125 is an attractive screening test for ovarian cancer because it is readily available and noninvasive. Levels of this antigen are elevated in approximately 90% of women with stage II, III, and IV ovarian cancer, but in only 50% of women with stage I disease.[5,6] Moreover, the test’s lack of specificity limits its use, as CA-125 levels are also elevated in many common benign conditions, including liver disease, fibroids, endometriosis, and ovulation. In a study of 1,010 postmenopausal women, 31 were found to have a CA-125 level > 30 IU/mL, and one of these 31 was diagnosed with stage IA ovarian cancer. The specificity of the serum CA-125 test was 97%.[7] In a case-control study using stored serum from 20,305 blood donors, 37 ovarian cancers were diagnosed over 15 years of follow-up. The sensitivity of the CA-125 level to detect these cancers was only 24%, and specificity, 96%.[8] Skates et al observed that women with ovarian cancer are more likely than women without ovarian cancer to have increasing CA-125 levels over time.[9] Researchers at St. Bartholomew’s Hospital are investigating the rate of change of the CA-125 level in serial determinations, to see if the test’s specificity improves. Preliminary data suggest that the rate of change of the CA-125 level has a sensitivity of 83% and specificity of 99.7% among postmenopausal women, although these data are derived from only six cases of ovarian cancer in the cohort.[9]

**Other Tumor Markers**

- **Lysophosphatidic acid (LPA)** is another tumor marker that is reportedly increased in the serum of women with ovarian cancer. The LPA level may be elevated more often than the CA-125 level in early-stage ovarian cancer. In one small study, serum LPA was elevated in 9 of 10 women with stage I cancer, whereas CA-125 levels were increased in only 2 of 9 cases.[10] In more advanced ovarian cancer, LPA has not been shown to be more sensitive than CA-125.

- **Macrophage–colony-stimulating factor (M-CSF)** levels are reported to be complementary to CA-125 levels in detecting ovarian cancer. Among 25 patients with known ovarian cancer and normal CA-125 levels, M-CSF was elevated in 56%. Elevated M-CSF levels were found in 31% of 29 women with normal CA-125 levels and positive findings for cancer at second-look surgical evaluation.[11]
Serum OVX-1 is another tumor marker that may be elevated among patients with ovarian cancer. In one study of patients with normal CA-125 levels who underwent second-look laparoscopy after primary treatment for ovarian cancer, 59% had elevated OVX-1 levels. However, another study found that only 65% of 46 patients with stage I ovarian cancer had elevated OVX-1 levels. Currently, stability and assay reliability problems make serum OVX-1 levels difficult to adapt for screening.

**Combination of serum markers** can increase the sensitivity of serum testing for the presence of ovarian cancer but at the expense of decreased specificity.

### Sonography as a Screening Tool

**Transabdominal pelvic sonography** was evaluated as a screening tool in 5,540 women in England. Each woman was to undergo three annual sonographic evaluations. A total of five ovarian cancers were detected, three of which were borderline tumors. The specificity of the test was 94.6%, but the PPV was only 2.6%. More than 25% of the false-positive sonograms had no ovarian pathology at exploration, and 74.3% had benign ovarian abnormalities. With this approach, 51 surgical explorations were required for each cancer found.

**Transvaginal sonography** provides a clearer morphologic assessment of the ovaries, compared to pelvic ultrasound. In a study of 1,300 postmenopausal women, 33 had abnormal sonograms, and 27 agreed to surgical exploration. Of these 27 women, 2 were found to have stage IA ovarian cancer. A larger study of 3,220 postmenopausal women used a specific morphology index to determine whether the sonogram was considered abnormal. In this study, 44 women had morphologic index-defined abnormalities. At laparotomy, 3 of the 44 were found to have ovarian cancer.

These promising results, with only 15 laparotomies required for each cancer found, led to a larger study of 8,500 women. Women with abnormal transvaginal ultrasounds underwent the procedure again within 4 to 6 weeks. Those with persistent abnormalities had a pelvic examination, serum CA-125 testing, color Doppler transvaginal ultrasound, and morphologic index assessment. Persistent abnormalities that required surgical evaluation were found in 121 women on transvaginal ultrasound. Of these 121 women, 8 had ovarian cancer, 5 of which were epithelial ovarian cancers (4 of the 5 were stage I or II), and 3 of which were granulosa cell tumors. In this study, the PPV was lower, with three epithelial ovarian cancers found among the 121 women requiring surgical exploration for abnormal transvaginal sonograms.

Lack of specificity, particularly in premenopausal women, is a major problem in using transvaginal sonography for screening the general population, with specificity reported as 98.1% to 98.7%. Of 776 women screened, 43 had an abnormal sonogram. At surgical evaluation, three stage IA ovarian cancers were detected, with one being a borderline tumor. The PPV was 7.7%.

**Transvaginal sonography with color Doppler** may improve the specificity of sonographic screening for ovarian cancer, based on the premise that the vascularity of malignant tissue has a lower impedance to blood flow than benign tissue. This combination of imaging techniques was evaluated in 14,317 women, and all adnexal masses were investigated surgically, independent of the Doppler impedance results. Among the 680 women who required surgical evaluation, ovarian malignancies were found in 56. Of these 56 malignancies, 54 had low impedance on Doppler. Adding Doppler imaging to transvaginal sonography decreased sensitivity to 96.4%, but increased specificity to 99.8%.

In a study of 1,601 women with a family history of ovarian cancer who referred themselves for screening, Bourne et al found that 61 had abnormal sonograms, based on morphologic and Doppler characteristics. All 61 underwent surgical exploration. Ovarian cancer was found in six; three of these six were borderline tumors, and one was stage III. Thus, the PPV for sonography with Doppler for detecting invasive ovarian cancer, even in this higher-risk population, remained low.

Karlan et al summarized five of the largest studies of sonography for the detection of ovarian cancer. These trials used various forms of sonographic imaging, including transabdominal sonography, transvaginal sonography, and color Doppler. Taken together, the five trials enrolled a total of 11,283 women. Surgical evaluation by laparotomy was required in 486 women, with 22 ovarian cancers found. Of these, 13 were stage I, and 5 of the 13 were invasive. The overall specificity was 95.8%, and the PPV was 3.1%.

An updated report by van Nagell et al was published recently. Transvaginal sonography was performed annually from 1987 to 1999 in women over 50 years old as well as in women over 30 with...
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a family history of ovarian cancer. Women with abnormal sonograms had a repeat sonogram 4 to 6 weeks later. Women with persistently abnormal scans then had a third sonogram with morphology indexing and Doppler flow, and a serum CA-125 test. Among 14,469 women, 180 (1.2%) had sonographic findings requiring surgical evaluation. Ovarian cancer was found in 17; 11 were stage I, 3 were stage II, and 3 were stage III.

Among patients with normal screening sonograms, four developed ovarian or peritoneal cancer within 12 months of a normal sonogram (false-negative screening test results). In this population of women, annual transvaginal sonography, with work-up of abnormal sonograms as specified above, yielded a sensitivity for ovarian cancer of 81%, specificity of 98.9%, and PPV of 9.4%. The sensitivity for detecting stage I epithelial ovarian cancer (excluding the borderline and granulosa cell tumors) was 31%.

Serum Test/Imaging Combinations

Combinations of serum tests and imaging hold promise for improving specificity. In the previously mentioned study of 1,010 postmenopausal women, the specificity increased to 99.8% when sonography was performed in the 31 women with elevated CA-125 levels, and surgical intervention was limited to those with abnormal findings on both tests.

In a subsequent study, 22,000 postmenopausal women had a CA-125 screening test, and those with levels > 30 IU/mL (n = 340) underwent sonography. Sonographic abnormalities were seen in 41 women, who then underwent surgical investigation. Of these 41 women, 11 had ovarian cancer (3 had stage I, 1 had stage II, 7 had stage III or IV). Among the remaining 21,959 women whose screening tests did not reveal an abnormality, 8 subsequently developed ovarian cancer. Thus, the sensitivity of the combination of CA-125 > 30 IU/mL and an abnormal sonogram was 78.6% at 1 year and 57.9% at 2 years, although specificity was 99.9%, and PPV was 26.8%.

Einhorn studied 5,550 women over 40 years old with a serum CA-125 measurement and, in those with elevated CA-125 levels, a sonogram. Of the 175 women who had an elevated CA-125, 6 were found to have ovarian cancer. Importantly, three women with normal CA-125 screening levels were subsequently diagnosed with ovarian cancer. Among the women in the study 50 years of age or older, the specificity of a CA-125 > 35 IU/mL was 98.5%; for those aged 40 to 49 years, the specificity was 94.5%. The PPV of an elevated CA-125 plus an abnormal sonography was 50% among women over age 50 years.

Outcomes of Ovarian Cancer Screening

The studies described above demonstrate that it is possible to detect early-stage ovarian cancer with currently available screening tests. Among these, the transvaginal sonogram with color Doppler has fairly good sensitivity and specificity. However, the low prevalence of the disease, even among self-referred women with positive family histories, make its PPV too low for use in the general population. The CA-125 test alone lacks specificity, particularly in premenopausal women, and may lack sensitivity for early-stage disease. Requiring that both the CA-125 level and the sonogram be abnormal sacrifices sensitivity and only achieves a high PPV among postmenopausal women. Furthermore, even if ovarian cancer is detectable, a screening test should ideally be associated with a decrease in mortality before it is widely recommended to the general population. To demonstrate a reduction in mortality would require a randomized, controlled trial, in which a control group does not receive screening. Researchers estimate that such a trial would have to enroll more than 100,000 women in each group to demonstrate a 30% decrease in mortality.

In a pilot trial, 22,000 postmenopausal women were randomly assigned to screening vs no screening. Investigators used a combined approach, in which postmenopausal women were offered annual CA-125 measurement for 3 years. Those with CA-125 > 30 IU/mL underwent pelvic sonography (transabdominally in the first year of the study, then transvaginally for all subsequent enrollees). Elevated CA-125 levels were found in 468 women. Those with both an elevated CA-125 and an abnormal sonogram underwent surgical evaluation.

This approach detected six cancers among 29 women who required surgical evaluation in the screened group during the 3 years of screening; 10 additional women developed ovarian cancer in the 8 years following their screening. In the no-screening group, 20 women developed ovarian cancer. The PPV of this screening strategy was 20.7%. There was no significant difference in overall mortality between the screened women and those who had not been screened.

The difference in the percentage of early-stage ovarian cancers in each group did not reach
statistical significance (31.3% of screened women developed stage I/II disease vs 10.0% of women who were not screened, \(P = .17\)). However, women with ovarian cancer in the screened group had a longer median survival than did women with ovarian cancer in the no-screening group (72 vs 42 months, \(P = .011\)). This observed difference may be confounded by lead-time bias, rather than representing a true benefit from screening.

Because of the lack of a large enough randomized trial, modeling has been used to assess the impact of screening for ovarian cancer in the general population. A decision analysis model, incorporating estimates of test sensitivity, specificity, and disease prevalence in the general population, showed that the use of transvaginal sonography and CA-125 measurement to screen asymptomatic 40-year-old women would, on average, increase life-expectancy by less than 1 day.[29] Table 2 provides an overview of the larger trials conducted in ovarian cancer screening.

**Ovarian Cancer Screening in High-Risk Women**

Despite the lack of data demonstrating a survival benefit from screening for ovarian cancer in the general population, it is recommended that women with germline mutations of **BRCA1** or **BRCA2** undergo screening, because the prevalence of cancer among this population is higher, with estimates of lifetime risk ranging from 16% to 65%.[30-32] Prophylactic oophorectomy may be considered at completion of childbearing or by age 45 years.[33] A screening program that includes a periodic pelvic examination, transvaginal sonography, and measurement of CA-125 levels is recommended until oophorectomy is performed, and for women who do not elect oophorectomy.[34] Women with a strong family history of ovarian and/or breast cancer (generally three or more affected blood relatives), or a personal history of breast cancer at a young age and a first- or second-degree relative with breast or ovarian cancer, are also at increased risk of carrying a **BRCA** mutation, and therefore may be appropriate candidates for screening. Women of Ashkenazi Jewish descent with a personal history of early-onset breast cancer, and/or a family history of early-onset breast and/or ovarian cancers, are also at increased risk.

Screening may be considered for women in these groups, regardless of whether they have elected to have genetic testing. However, high-risk women who choose ovarian cancer screening should be made aware that there are no data demonstrating that screening will detect early cancer or prolong their lives.

A decision model assessed the benefits of genetic testing for three specific **BRCA1/BRCA2** mutations among unaffected Ashkenazi Jewish women, with ovarian cancer screening and/or prophylactic surgery offered to mutation carriers. The model assumed that **BRCA1/BRCA2** mutation carriers had a 16% risk of developing ovarian cancer by age 70 years. The model estimated that performing twice-yearly sonography, pelvic examination, and CA-125 testing for mutation carriers would add 6 days (95% probability interval: 3–8 days) to overall survival, and prophylactic oophorectomy would add 11 days (95% probability interval: 4–25 days).[35] Prospective data are needed regarding actual risk of ovarian cancer, the sensitivity and specificity of screening strategies among high-risk women, and the efficacy of prophylactic surgery for risk reduction.

**What We Need to Know**

**General Population**

For the general population, the most pressing issue remains whether screening for ovarian cancer can decrease mortality. Three randomized trials are currently underway.

The Prostate, Lung, Colon, Ovary trial is a randomized trial of screening vs no screening for these cancers. Approximately 74,000 women over age 60 years will be randomized to CA-125 testing, sonogram, and clinical examination or to a no-screening control group. This sample size will require 16 years of follow-up in order to have an 80% power to detect a 30% decrease in mortality. [National Institutes of Health, unpublished data]

The second study, the St. Bartholomew's study, is using the combination-screening strategy employed in the pilot study of 10,000 women. In this trial, 120,000 postmenopausal women over age 50 years will be randomized to annual CA-125 screening or to a no-screening control group. Women with a CA-125 pattern suggestive of ovarian cancer will have a sonogram. Those with abnormal sonograms will undergo surgical evaluation. This study is designed to have an 80% power to detect a 30% reduction in mortality, with completion expected in 7 years.

A third study, the European Multicentre Study, aims to enroll and randomize 120,000 postmenopausal women to transvaginal sonography either every 3 years or every 1.5 years or to a
no-screening control group. Because the prevalence of this disease in the general population is so low, another reasonable approach may be to focus on developing new screening techniques (eg, novel imaging methods, novel tumor markers) that have higher sensitivity and specificity than the serum CA-125 test and sonography. In addition, general population research is needed on preventive measures, and better identification of epidemiologic factors associated with nonhereditary ovarian cancer.

**High-Risk Population**

For the group of women with a higher disease prevalence, screening is recommended by expert opinion in the absence of a demonstrated mortality benefit. Thus, we must address the issues associated with the application of such recommendations to all high-risk women.

The issue of how screening affects quality of life and psychological functioning over time is important, since prior studies have shown that false-positive test results may be associated with increased distress[37] in the short-term.[38-40] In high-risk women, for whom long-term serial screening is recommended, the probability of receiving a false-positive result at some point is high. We do not know whether screening will alleviate or exacerbate anxiety about ovarian cancer risk, nor do we know whether offering screening to all high-risk patients will alter the expected distribution of ovarian cancers by stage (ie, detect early-stage cancers). Moreover, we do not know whether the number of women requiring surgical evaluation for benign disease due to false-positive test results will be higher or lower than that in the general population.

Ovarian screening studies have not formally addressed costs, either personal or societal. Costs have been modeled using cost and outcome estimates from the literature,[41,42] but actual medical resource use data are needed for both high-risk women and the general population in order to make reliable resource allocation decisions. In the high-risk population, we do not know whether women undergoing recommended screening will incur large personal financial burdens. The impact of screening program participation on their insurability and employability is also unknown. Preliminary data from an ongoing prospective study of ovarian cancer screening in high-risk women at Memorial Sloan-Kettering Cancer Center suggest that anxiety may be exacerbated by false-positive test results, and that worsening anxiety may interfere with compliance with screening recommendations. Furthermore, screening high-risk women inevitably involves other major issues pertinent to this population, including genetic counseling and genetic testing, and the application of these results (if the patient chooses to share them) to the screening recommendations; prophylactic mastectomy and prophylactic oophorectomy efficacy, recommendations, and timing of surgery; screening recommendations for sisters, mothers, and daughters; oral contraceptive use, tamoxifen (Nolvadex) use (and management of endometrial thickness findings on transvaginal sonograms performed for ovarian assessment), and hormone replacement therapy (particularly for young women who elect prophylactic oophorectomy).

Physicians who offer ovarian cancer screening should be prepared to discuss all the issues facing high-risk women, and appropriate supportive services should be available. Women should be carefully counseled about the risk of false-positive test results and should understand that repeat evaluations are often needed. In premenopausal women who are undergoing screening, both the transvaginal sonogram and the CA-125 test should be performed within the first 10 days of the menstrual cycle, in order to decrease the likelihood of false-positive results due to ovulatory changes.

**Conclusions**

Screening for ovarian cancer cannot be recommended for the general population of women because disease prevalence is too low for current screening modalities to have reasonable specificity and positive predictive value. Physicians should record family histories carefully to find women who may be at higher risk of developing ovarian cancer and who may, therefore, consider genetic counseling/testing and ovarian cancer screening.

Screening with serial transvaginal sonography[43]with or without Doppler imaging[44]and CA-125 measurement is recommended for those at high risk for ovarian cancer. Physicians offering ovarian cancer screening should be prepared to address other issues pertinent to high-risk women, such as genetic counseling/testing, hormone replacement therapy, and prophylactic risk-reducing surgery. High-risk women should be encouraged to participate in prospective screening cohort studies that may answer important questions, such as the stage distribution of cancers detected, the number of false-positive screening test results, the impact of screening on quality of life and psychological distress, and the financial burden (both societal and personal) incurred by screening.
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