The Role of the Obstetrician–Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk

ABSTRACT: Ovarian cancer is the second most common type of female reproductive cancer, and more women die from ovarian cancer than from cervical cancer and uterine cancer combined. Currently, there is no strategy for early detection of ovarian cancer that reduces ovarian cancer mortality. Taking a detailed personal and family history for breast, gynecologic, and colon cancer facilitates categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer. Women with a strong family history of ovarian, breast, or colon cancer may have hereditary breast and ovarian cancer syndrome (BRCA mutation) or hereditary nonpolyposis colorectal cancer (Lynch syndrome), and these women are at increased risk of developing ovarian cancer. Women with these conditions should be referred for formal genetic counseling to better assess their cancer risk, including their risk of ovarian cancer. If appropriate, these women may be offered additional testing for early detection of ovarian cancer. The use of transvaginal ultrasonography and tumor markers (such as CA 125), alone or in combination, for the early detection of ovarian cancer in average-risk women have not been proved to reduce mortality, and harms exist from invasive diagnostic testing (eg, surgery) resulting from false-positive test results. The patient and her obstetrician–gynecologist should maintain an appropriate level of suspicion when potentially relevant signs and symptoms of ovarian cancer are present.

Recommendations and Conclusions
The American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology offer the following recommendations and conclusions:

- Epithelial ovarian cancer is most commonly detected in an advanced stage (65% of cases are stage III or stage IV) when the cure rate is only 18%.
- Early stage (localized) ovarian cancer is associated with improved survival.
- Taking a detailed personal and family history for breast, gynecologic, and colon cancer facilitates categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer.
- The patient and her obstetrician–gynecologist should maintain an appropriate level of suspicion when potentially relevant signs and symptoms of ovarian cancer are present.
Background
Ovarian cancer is the second most common type of female reproductive cancer, and more women die from ovarian cancer than from cervical cancer and uterine cancer combined. Researchers estimated that in 2016, 22,280 women would be diagnosed with ovarian cancer and 14,240 women would die from this malignancy in the United States alone (1). Epithelial ovarian cancer is most commonly detected in an advanced stage (65% of cases are stage III or stage IV) when the cure rate is only 18% (2). In contrast, early stage (localized) ovarian cancer is associated with improved survival, and women with stage I disease have an 88% probability of cure (2). However, based on available data, the U.S. Preventive Services Task Force recommends against screening for ovarian cancer in asymptomatic women at average risk (3). The purpose of this Committee Opinion is to provide an evidence-based summary of the strategies for early detection of epithelial ovarian cancer in women at average risk of ovarian cancer. There currently is no strategy for early detection of ovarian cancer that reduces ovarian cancer mortality.

Determining Risk of Ovarian Cancer
Taking a detailed personal and family history for breast, gynecologic, and colon cancer facilitates categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer. The American College of Obstetricians and Gynecologists’ Committee Opinion No. 478, Family History as a Risk Assessment Tool, discusses how best to take a relevant and detailed family history (4). Women with a strong family history of ovarian, breast, or colon cancer may have hereditary breast and ovarian cancer syndrome (BRCA mutation) or hereditary nonpolyposis colorectal cancer (Lynch syndrome) (5), and these women are at increased risk of developing ovarian cancer. Women with these conditions should be referred for formal genetic counseling to better assess their cancer risk, including their risk of ovarian cancer. If appropriate, these women may be offered additional testing for early detection of ovarian cancer. Hereditary breast and ovarian cancer syndromes are discussed in more detail in Practice Bulletin No. 103, Hereditary Breast and Ovarian Cancer Syndrome (5). The remainder of this Committee Opinion refers to women at average risk of developing ovarian cancer.

Early Detection of Ovarian Cancer in Average-Risk Women
The use of transvaginal ultrasonography and tumor markers (such as CA 125), alone or in combination, for the early detection of ovarian cancer in average-risk women have not been proved to reduce mortality. Harms exist from invasive diagnostic testing (eg, surgery) that result from false-positive test results (3). In light of current data, the U.S. Preventive Services Task Force recommends against screening asymptomatic women for ovarian cancer by ultrasonography, serum tumor markers, or pelvic examination (3). Combined-modality early detection strategies for ovarian cancer are being investigated actively. Because of the low prevalence of disease, incidence of a false-positive test result leading to invasive diagnostic interventions (eg, surgery and oophorectomy) may be unacceptably high. Additionally, the available tests and technologies have questionable ability to detect ovarian cancer at an early enough stage to ensure that treatment can reduce mortality. Together, these factors represent challenges to developing an effective test or algorithm for the early detection of ovarian cancer.

Transvaginal Ultrasonography
Transvaginal ultrasonography has been assessed as an early detection method for ovarian cancer under the premise that it may detect changes in ovarian size and morphology before signs or symptoms of cancer develop, and data show it to be ineffective. The ultrasound screening arm (n=50,623) of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (n=202,546) demonstrated that for every one woman with ovarian or peritoneal cancer detected by annual ultrasound screening, an additional 10 women had surgery based on a false-positive test result (6). The positive predictive value (PPV) of ultrasonography for the detection of ovarian cancer was extremely low, and the harms related to unnecessary surgeries resulting from false-positive test results outweighed any demonstrated benefits (3, 7). Additionally, the study showed that screening women at average risk of developing ovarian cancer with an annual transvaginal ultrasonography provided no mortality benefit compared with no screening (6).

Cancer Antigen 125 Serum Tumor Marker
The serum tumor marker CA 125 is the most extensively evaluated serum marker for the early detection of ovarian cancer. Initial studies showed that CA 125 levels were elevated in approximately 80% of women with epithelial ovarian cancer (8). However, subsequent studies have demonstrated that fixed CA 125 cutoff values for early-stage cancer detection have poor sensitivity and specificity (7, 9–11). The Risk of Ovarian Cancer Algorithm, which uses serially measured CA 125 levels and proprietary mathematical modeling to determine if an increase in levels should trigger referral for ultrasonography, has demonstrated a better PPV for detecting ovarian cancer when compared with fixed CA 125 cutoff values (12, 13). However, there is no evidence demonstrating that the use of a CA 125 assessment alone, with either a fixed cutoff value or serial measurement, has an acceptable PPV for ovarian cancer or that it reduces ovarian cancer mortality.

The U.S. Food and Drug Administration has approved laboratory panels of multiple tumor markers (including CA 125) to categorize women found to have
adnexal masses on imaging as low risk or high risk of ovarian malignancy (14–17). However, these panels have not been rigorously evaluated among asymptomatic women without adnexal masses and have not been shown to improve early detection and survival rates for ovarian cancer in average-risk women. Use of these markers for the management of adnexal masses is discussed in other publications (18).

**Combined Modality Early Detection Strategies**
Neither ultrasonography nor measurement of tumor markers has demonstrated the sensitivity, specificity, and PPV necessary to justify use for early detection of ovarian cancer in women at average risk. In light of this, several large-scale, prospective randomized trials in the United States and the United Kingdom aim to address the utility of combined modality assessment for the early detection of ovarian cancer.

The U.S.-based Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial randomized 78,216 healthy average-risk women between the ages of 55 years and 74 years to receive either annual CA 125 testing (for 6 years) plus transvaginal ultrasonography (for 4 years) (tested group) or “usual care” (not offered this testing; however, many received annual pelvic examinations) (7, 19). After a median follow-up of 12.4 years, the ovarian cancer mortality rate was 3.1 deaths per 10,000 person-years in the tested group and 2.6 deaths per 10,000 person-years in the usual care group (19). The results provided solid evidence that using a baseline and annual measurement of serum marker CA 125 with a fixed cutoff (35 U/mL) in combination with transvaginal ultrasonography as a strategy for early assessment does not result in a decrease in ovarian cancer mortality. In addition, the ongoing United Kingdom Collaborative Trial of Ovarian Cancer Screening randomized 202,638 healthy, average-risk, postmenopausal women between the ages of 50 years and 74 years to receive no screening, annual ultrasonography, or multimodal screening using a combination of CA 125 measurement (interpreted using the Risk of Ovarian Cancer Algorithm) and ultrasonography triggered by a Risk of Ovarian Cancer Algorithm score signifying increased risk (20). Although this study showed that multimodal screening using the Risk of Ovarian Cancer Algorithm for detection of ovarian cancer was superior to using fixed CA 125 cutoffs (PPV=35.1%), the published 14-year follow-up data have shown a nonsignificant reduction of ovarian cancer mortality with multimodal screening (15% mortality reduction, 95% confidence interval, –3 to 30 [reflecting a 3% increase in mortality up to a 30% decrease in mortality], P=.1) when compared with no screening. However, the authors of this trial state that “further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening” (6). In 2016, the Ovarian Cancer Research Fund Alliance convened a meeting of stakeholders, including clinicians, scientists, professional organizations, and advocacy groups, to discuss the results of the trial. The consensus of the panel was that it is premature to recommend multimodal screening for the early detection of ovarian cancer at this time (21).

**Direct-to-Consumer Marketing of Ovarian Cancer Screening Tests**
Ovarian cancer screening tests and early detection tests, such as those using the Risk of Ovarian Cancer Algorithm and laboratory panels of multiple tumor markers, are being marketed directly to women. At this time, there is insufficient evidence to support the use of any of these tests or algorithms for the early detection of ovarian cancer in average-risk women. Women considering purchasing these tests, which are currently not approved nor cleared by the U.S. Food and Drug Administration for ovarian cancer screening and are not financially covered by medical insurance, should be counseled on the risks of such tests.

**Evaluation of Average-Risk Women With Symptoms or Signs**
The patient and her obstetrician–gynecologist should maintain an appropriate level of suspicion when potentially relevant signs and symptoms of ovarian cancer are present. A case–control study demonstrated that women with more than 12 days per month of new onset (less than 12 months’ duration) symptoms, including an increase in abdominal size or bloating, pelvic or abdominal pain, or difficulty eating or feeling full quickly had increased odds of having ovarian cancer compared with women without these symptoms (22). The study suggested that women with these symptoms should be evaluated, and ovarian cancer should be included in the differential diagnosis. Women and obstetrician–gynecologists should be aware that although these vague symptoms are more common in women with ovarian cancer, the vast majority of women with these symptoms will not have ovarian cancer because these symptoms can be caused by other more common conditions.

**References**


Committee Opinion No. 716


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ISSN 1074-981X

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