

Ca 125, A Poor Screening Test for Ovarian Cancer

Several times a week I am asked if routine Ca 125 “screening” is something that I would advise my patients to have done.

Unfortunately, there are no good screening tests for ovarian cancer available. This statement includes Ca 125 testing. The key to this statement lies in what constitutes a good “screening” test. To qualify as a good screening test, a test must meet the following criteria:

1. The test must be easy to perform
2. The test must be relatively inexpensive
3. The test must be highly sensitive
4. The test must be highly specific

Ca 125 testing for “screening” purposes has been very carefully looked at by researchers. Ca 125 blood testing is certainly easy to do, and the cost is not terribly expensive. The “sensitivity” of any screening test relates to how likely it will be that the individuals reported to be in the “screen positive” group will include most of the individuals who really have the problem being tested for. “Highly sensitive” means that the test will be reported as negative only when the individual being tested really doesn’t have the disease being screening for. Another way of saying this is that the “false negative” rate will be very low. In fact, Ca 125 testing is very sensitive. So far so good, and you’re thinking this is a great test. The “specificity” of any screening test relates to how many of the individuals reported as being in the “screen positive” group in reality don’t have the problem being tested for. These are known as “false positive” results. The problem Ca 125 screening comes with this last item. The specificity of Ca 125 screening is poor. The test will come back with elevated or “positive” results because of many other much more common, benign conditions besides ovarian malignancies. The “false positive” rate for Ca 125 testing is unacceptably high. For every woman who has a “true

positive”, meaning she really has the disease we are trying to identify, there will be about 50 “false positive” women. The problem becomes what to do with those “false positive” individuals. Once an elevated Ca 125 level is recorded in a woman’s record, she must be subjected to a complete evaluation to establish her real diagnosis. Remember, the Ca 125 level was just a screening test to see who needed further testing. That testing, includes ultimately, surgical exploration to make sure the woman either really does or doesn’t have the disease. Some of those falsely positive women will develop complications from the evaluation process, or at the least they will suffer emotionally and psychologically from going through what was really an unnecessary procedure.

Gene Wilder and others have done a great job of letting women know that a test is available, but they haven’t done the whole job by explaining why Ca 125 isn’t any good as a screening tool. I understand their grief and their need to try to make something good come out of their tragic loses. Their motives are good, but they are misguided.

If doctors had a test for the early diagnosis of these diseases that was truly appropriate to be used as a screening tool, we’d offer it to our patients in a heart beat. I don’t know of a single doctor who wouldn’t welcome the availability of a good screening test for ovarian cancer. I, and all responsible physicians wish there were such a screening tool for ovarian and primary peritoneal cancer. Unfortunately wishing it so doesn’t make it so.

None the less, if any woman insists upon having a Ca 125 test done I will do the test after I’ve explained all of the above to her. She must know in advance that she may have a “false positive” result that will require a full investigation, including operative exploration. I will try to discourage her from insisting upon

getting tested, but I respect and accept her right to make the final decision.

See below for additional scientific materials and references related to this important subject.



U.S. Preventive Services Task Force

Recommendation Statement

Screening for Ovarian Cancer: Recommendation Statement

U.S. PREVENTIVE SERVICES TASK FORCE

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). EB CME is clinical content presented with practice recommendations supported by evidence that has been systematically reviewed by an AAFP-approved source. The practice recommendations in this activity are available online at <http://www.ahrq.gov/clinic/uspstf/uspsovar.htm>.

This is one in a series excerpted from the Recommendation Statements released by the U.S. Preventive Services Task Force (USPSTF). These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and chemoprevention. The complete statement is available in [HTML](#) and [PDF](#) formats through the AFP Web site at <http://www.aafp.org/afp/20050215/us.html>. This statement is part of AFP's CME. See "[Clinical Quiz](#)" on page 647.

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for ovarian cancer and the supporting scientific evidence, and updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services, 2d ed.*¹ In 1996, the USPSTF recommended against routine screening for ovarian cancer (D recommendation).¹ Since then, the USPSTF criteria to rate the strength of the evidence have changed.² Therefore, this recommendation statement has been updated and revised based on the current USPSTF methodology and rating of the strength of the evidence. Explanations of the current task force ratings and strength of overall evidence are given in *Tables 1 and 2*, respectively.

The complete information on which this statement is based, including evidence tables and references, is available in the brief evidence update³ on this topic on the USPSTF Web site

(<http://www.preventiveservices.ahrq.gov>). The recommendation statement and brief evidence update also are available in print from the Agency for Healthcare Research and Quality Publications Clearinghouse (telephone: 1-800-358-9295; e-mail: ahrqpubs@ahrq.gov). The recommendation also is posted on the Web site of the National Guideline Clearinghouse (<http://www.guideline.gov>).

This recommendation statement was first published in *Ann Fam Med* 2004;2:260-2.

Summary of Recommendation

The USPSTF recommends against routine screening for ovarian cancer. **D recommendation.**

The USPSTF found fair evidence that screening with serum CA-125 level or transvaginal ultrasound can detect ovarian cancer at an earlier stage than it can be detected in the absence of screening; however, the USPSTF found fair evidence that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer. Because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, there is fair evidence that screening could likely lead to important harms. The USPSTF concluded that the potential harms outweigh the potential benefits.

Clinical Considerations

- There is no existing evidence that any screening test, including CA-125, ultrasonography, and pelvic examination, reduces mortality from ovarian cancer. Furthermore, existing evidence that screening can detect early-stage ovarian cancer is insufficient to indicate that this earlier diagnosis will reduce mortality.
- Because there is a low incidence of ovarian cancer in the general population (age-adjusted incidence of 17 per 100,000 women), screening for ovarian cancer is likely to have a relatively low yield. The great majority of women with a positive screening test will not have ovarian cancer (i.e., they will have a false-positive result). In women at average risk, the positive predictive value of an abnormal screening test is, at best, approximately 2 percent (i.e., 98 percent of women with positive test results will not have ovarian cancer).
- The positive predictive value of an initially positive screening test would be more favorable for women at higher risk. For example, the lifetime probability of ovarian cancer increases from about 1.6 percent in a 35-year-old woman without a family history of ovarian cancer to about 5 percent if she has one relative and 7 percent if she has two relatives with ovarian cancer. If ongoing clinical trials show that screening has a beneficial effect on mortality rates, then women at higher risk are likely to experience the greatest benefit.

Discussion

Ovarian cancer is the fifth leading cause of cancer death among women in the United States, accounting for an estimated 25,400 new cases and 14,300 deaths in 2003.⁴ Several risk factors are

associated with ovarian cancer. Family history increases the risk for ovarian cancer: having one first- or second-degree relative with ovarian cancer increases risk by about threefold.⁵ Carriers of the BRCA1 or BRCA2 gene mutations also are at increased risk.⁶ The risk for developing ovarian cancer is reduced with oral contraceptive use and pregnancy of any duration.⁷ Some studies have shown that postmenopausal women taking estrogen may be at increased risk for developing ovarian cancer.^{8,9}

Most women with ovarian cancer have nonlocalized disease at the time of diagnosis.⁴ A randomized controlled trial (RCT) using multimodal screening (CA-125 screening, followed by ultrasonography in patients with abnormally elevated levels) reported that 50 percent of patients with ovarian cancer in the screened group were in stage I, compared with only 5 percent in the control group.^{3,10} This difference was not statistically significant. Two large cohort studies using transvaginal ultrasonographic screening reported that 59 to 65 percent of ovarian cancers were diagnosed in stage I.^{11,12} However, there is no evidence that detecting earlier-stage tumors through screening leads to a decrease in ovarian cancer-specific mortality.

Establishing the true sensitivity of CA-125 or ultrasonography is limited by several factors. The studies assessing the accuracy of screening tests have used different thresholds to define an elevated CA-125 level and different lengths of clinical follow-up, and have included small numbers of patients. In women at average risk for ovarian cancer, using thresholds of 30 U per mL or 35 U per mL, the one-year follow-up sensitivity of CA-125 screening, followed by ultrasonography, has been reported to be about 80 percent; the specificity is nearly 100 percent.¹³⁻¹⁵ However, using a similar CA-125 threshold for women at high risk for ovarian cancer, the sensitivity would be reduced to 50 percent. The estimated sensitivity of annual transvaginal ultrasonography at one-year follow-up is 88 percent (95 percent confidence interval [CI], 47 to 100 percent); the specificity is estimated to range from 97 to 99 percent.¹⁶ There is conflicting evidence as to whether adding color Doppler imaging to ultrasonographic screening can reduce the rate of false-positive test results.^{17,18} There are few data available to determine the sensitivity and specificity of successive rounds of screening.

There is a significant potential for harms associated with screening for ovarian cancer, although there are few data to assess the magnitude of harms from screening, such as needless surgery or increased anxiety. A study by the British Health Technology Assessment program estimated that screening a hypothetical cohort of 10,000 women aged 50 to 64 for ovarian cancer, using either annual CA-125 or twice-yearly transvaginal ultrasonography (assuming specificities of 97 and 93 percent, respectively), would result in 300 women (using CA-125) or 350 women (using ultrasonography) who do not have ovarian cancer being recalled each year for further assessment, resulting in potential distress and anxiety in otherwise healthy women.¹⁶ Of these, 20 (using CA-125) or 65 (using ultrasonography) women without ovarian cancer would undergo surgery each year. For women at average risk for ovarian cancer, the positive predictive value of an abnormal screening test is, at best, approximately 2 percent. On the other hand, the potential benefits of screening (based on this model's optimistic assumption that earlier treatment leads to a 40 percent

mortality reduction) would yield a maximum of four additional cancers detected per year and would result in 1.5 additional five-year survivors for each year of screening.

Although no RCT of screening for ovarian cancer with mortality outcomes in the general population has yet been completed, at least three such RCTs are currently in progress: the United Kingdom Collaborative Trial of Ovarian Cancer Screening; the National Institutes of Health Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and the European Randomized Trial of Ovarian Cancer Screening.¹⁹⁻²¹

Recommendations of Others

Routine screening for ovarian cancer is not recommended by any medical organization. The American Cancer Society states that women with a strong family history of this disease may be screened, but transvaginal ultrasonography and CA-125 are not recommended in women without known strong risk factors for ovarian cancer.²² Instead of routine screening, the American College of Obstetricians and Gynecologists suggests that generalist obstetrician-gynecologists remain vigilant for the early signs and symptoms of ovarian cancer, such as abdominal or pelvic pain and unexplained weight loss, and that these symptoms be evaluated by pelvic examination, CA-125, or ultrasonography.²³ The Canadian Task Force on Preventive Health Care recommended against screening asymptomatic pre- and post-menopausal women in 1994.²⁴ The Canadian task force also found insufficient evidence to recommend for or against screening high-risk women with a family history of ovarian cancer, but noted that expert opinion suggested these women be referred to an academic health center for regular combination screening.

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The U.S. Preventive Services Task Force recommendations are independent of the U.S. government. They do not represent the views of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the U.S. Public Health Service.

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TABLE 1

USPSTF Recommendations and Ratings

The USPSTF grades its recommendations according to one of five classifications (A, B, C, D, or I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The

USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms

- B.** The USPSTF recommends that clinicians provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.
- C.** The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
- D.** The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.
- I.** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

USPSTF = U.S. Preventive Services Task Force.

TABLE 2

USPSTF Strength of Overall Evidence

The USPSTF grades the quality of the overall evidence for a service on a three-point scale (good, fair, or poor).

Good:	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair:	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.
Poor:	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

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