Screening for Ovarian Cancer: Evidence Update for the U.S. Preventive Services Task Force Reaffirmation Recommendation Statement

Prepared by:
Mary B. Barton, MD, MPP
Scientific Director
Center for Primary Care, Prevention, and Clinical Partnerships
Agency for Healthcare Research and Quality
Rockville, MD 20850

Kenneth Lin, MD
Medical Officer
Center for Primary Care, Prevention, and Clinical Partnerships
Agency for Healthcare Research and Quality
Rockville, MD 20850

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Abstract

Background: Ovarian cancer has the highest mortality rate of all gynecologic malignancies, and was the fifth leading cause of cancer death among women in 2004.

Purpose: To perform a literature search for new, substantial evidence that would inform the reaffirmation of the U.S. Preventive Services Task Force's recommendation on screening for ovarian cancer.

Data Sources: We searched the MEDLINE and Cochrane databases. The searches were limited to English-language articles on studies of adult humans (age >18 years) that were published between July 1, 2002 and January 15, 2008 in core clinical journals.

Study Selection: For the literature on benefits of screening, we included controlled trials as well as systematic reviews and meta-analyses. For harms, we included controlled trials, cohort studies, case-control studies, and case series, as well as systematic reviews and meta-analyses. Two reviewers independently reviewed titles, abstracts, and full articles for inclusion.

Data Extraction: No new evidence was found on the benefits of screening for ovarian cancer. A single reviewer extracted data from studies on the harms of screening.

Data Synthesis: No new evidence was found on the benefits of screening for ovarian cancer. New evidence on the combination of ultrasonography and cancer antigen-125 blood tests for screening suggests that abnormal test results may result in surgery for a substantial proportion of women who do not have cancer.

Limitations: The search strategy employed may have missed some smaller studies on the benefits and harms of screening for ovarian cancer.

Conclusion: No new evidence was found on the benefits of screening for ovarian cancer. Screening asymptomatic women can result in unnecessary interventions, including surgery.

INTRODUCTION

In 2004, ovarian cancer was the eighth leading cause of cancer diagnosis in women, and the fifth leading cause of cancer death.[1] Ovarian cancer is a frequently fatal malignancy; in 2008, there were an estimated 15,520 deaths in the United States due to this disease, and 21,650 new cases.[2] Ultrasonography of the pelvis and biochemical assessment for cancer antigen (CA)-125 remain under investigation in two ongoing trials assessing the efficacy of screening for ovarian cancer in average-risk women, while researchers continue to search for other markers that might prove useful in the early identification of ovarian cancer.

The U.S. Preventive Services Task Force (USPSTF) released in 2004 a recommendation against routine screening for ovarian cancer (grade D recommendation).[3] At that time, the USPSTF found fair evidence that screening could detect disease at an earlier stage than waiting for the presentation of symptoms; however, the USPSTF also found fair evidence that the potential impact on mortality of early detection and treatment of ovarian cancer was likely no more than small. The USPSTF had little data on harms, but instead described the theoretical presence of important harms from screening.

In 2008, the USPSTF decided to update its recommendation on screening for ovarian cancer. Noting the evidence base available at the time of the 2004 recommendation, and the fact that a large, high-quality study would be necessary to demonstrate important benefits to screening for ovarian cancer and thus overturn the existing recommendation, the USPSTF decided to undertake a reaffirmation update for this topic. The USPSTF performs reaffirmation updates for recommendation statements that remain USPSTF priorities, are within the scope for the USPSTF, and for which there is a compelling reason for the USPSTF to have a current recommendation statement. To assist the USPSTF in updating its 2004 recommendation on screening for ovarian cancer, staff at the Agency for Healthcare Research and Quality performed a literature search and consulted with subject area experts.

METHODS

The USPSTF developed two key questions to be addressed: 1) What are the benefits of screening for ovarian cancer in adult women? and 2) What are the harms of screening for ovarian cancer?

Data Sources

We performed literature searches of MEDLINE and the Cochrane library. In order to parallel the previous evidence review on this topic,[4] we used the same search terms that had been previously used: ovarian neoplasms, ovarian cancer, mass screening, physical examination, tumor markers, ultrasound imaging, and vaginal smears or pap smear. We included in our searches English-language studies of adult humans (age >18 years) that were published in core clinical journals between July 1, 2002 and January 15, 2008. Core clinical journals, formerly known as the Abridged Index Medicus, are a subset of 120 journals defined by the National Library of Medicine. We also checked reference lists of retrieved articles for possibly relevant studies.

Study Selection

One of two reviewers reviewed the titles and abstracts of retrieved studies; two reviewers independently read and assessed articles for abstraction based on inclusion and exclusion criteria. For the literature on benefits of screening, we included controlled trials as well as systematic reviews and meta-analyses. For harms, we included controlled trials, cohort studies, case-control studies, and case series, as well as systematic reviews and meta-analyses. We excluded editorials and guidelines.

Data Extraction

No studies were included for data abstraction on the benefits of screening for ovarian cancer. For data on the harms of screening, one reviewer abstracted information on sample size, number of patients with abnormal test results, and followup evaluation of abnormal tests, including surgical biopsy and cancer outcomes.

Data Synthesis and Analysis

Data from the included studies were not able to be synthesized due to heterogeneity in patient populations and study design, but are summarized qualitatively in narrative format.

Role of the Funding Source

The work of the USPSTF is supported by the Agency for Healthcare Research and Quality. No separate funding was used specifically for this study.

RESULTS

Our literature search returned 64 potentially relevant titles that were entered into a reference database. A total of 60 articles were excluded after title and abstract review, and two more were excluded after full article review. We excluded 18 studies not related to ovarian cancer, 34 studies that did not describe screening, two studies that described no relevant outcomes, two studies that described a high-risk or special patient population, and three studies that were an inappropriate study type. One additional report of a prospective screening study that was included in the evidence for harms was identified after a supplemental search of MEDLINE for publications by selected authors.

Evidence of the Benefits of Screening for Ovarian Cancer

No studies were found that provided data on the benefits of screening that met our inclusion criteria.

Evidence of the Harms of Screening for Ovarian Cancer

Three studies presented data on the harms of screening for ovarian cancer and met our inclusion

criteria.

Buys and colleagues report the results of the initial ovarian cancer screening round within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.[5] After random assignment to the screening arm, 28,816 women aged 55 to 74 years received transvaginal ultrasonography (TVU), CA-125 testing, or both. Baseline screening tests were first performed in 1993, and the last subject had baseline ovarian cancer screening in 2001. Followup of abnormal test results was at the discretion of the subject's personal physician. Ascertainment of followup and evaluation was performed by standardized review and abstraction of medical records for all women with positive screening test results.

Of the 28,519 women who had TVU performed, 1,338 had abnormal results (4.7 percent). Among women with abnormal TVU results, 535 (40 percent) underwent biopsy, for a yield of 22 neoplasms (13 invasive cancer cases and nine tumors of low malignant potential). The positive predictive value (PPV) of TVU was 1.6 percent for any neoplasm, and 1.0 percent if tumors of low malignant potential were excluded. Of the 28,803 women with baseline CA-125 tests performed, 402 had abnormal results (1.4 percent) and 62 biopsies were performed, yielding 16 neoplasms (15 invasive cancer cases and one tumor of low malignant potential). The PPV of CA-125 testing was 4.0 percent for any neoplasm, and 3.7 percent for invasive cancer only. In the subset of women with abnormal results on both tests, 34 (0.1 percent) underwent 27 biopsies and nine neoplasms were discovered (eight invasive cancer cases and one tumor of low malignant potential.) The PPV for the combined tests was 26.5 percent for any neoplasm and 23.5 percent for invasive cancer.

The proportions of biopsy results that were positive for invasive neoplasm were 2.4, 24.2, and 29.6 percent for TVU, CA-125, and combined testing, respectively. Overall, 570 (33.4 percent) women out of 1,706 who had an abnormal result on either test underwent surgical biopsy (325 laparotomy and 245 either laparoscopy or a vaginal approach). Of these 1,706 women, 541 (31.7 percent) had surgery without a diagnosis of cancer. The authors note that this represents abdominal surgery in nearly 2 percent of the 28,816 women who were screened upon entry to the PLCO trial. Also of note, the relative contribution of tumors of low malignant potential comprised 31 percent of total malignancies detected in the baseline round, while they represent only 15 percent of all ovarian cancer diagnoses recorded in the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Tumors of low malignant potential, or borderline tumors, have favorable 5- and 10-year survival at all stages.[6]

A study by Rufford and colleagues included women with symptoms, so it provides a different perspective of diagnostic assessment. They report on a pilot randomized trial in the United Kingdom, in which general practitioners were randomly assigned by practice, the study group had rapid access to ultrasonography and CA-125 testing via referral to a gynecological research center, and eligible women were older than age 45 years and had complained of symptoms previously reported to be associated with an ovarian cancer diagnosis, including abdominal pain or discomfort, abdominal bloating, indigestion, urinary frequency or incontinence, constipation, anorexia, weight loss, and back pain, among others.[7] Clinicians were encouraged to use their usual guideline-established referral procedure (i.e., referral to the local cancer unit) for women in whom there was a high suspicion of ovarian cancer. Followup was managed by the study unit.

Thirty nine of 79 practices in the study recruited 317 women between 2002 and 2005; 315 women were eligible and 290 attended screening. TVU was abnormal in 23 (7.9 percent) women and CA-125 tests were abnormal (>35 U/mL) in 13 (4.5 percent). Most women (33 of 36) with abnormal results on one or both tests repeated one or both tests over the following months. Only three women (representing 8 percent of women with an abnormal test result, or 1 percent of the 290 women referred for screening) had surgery to evaluate an ovarian abnormality. No malignancies were detected after a median followup of 23 months (range, 15–33 months).

An additional result of testing was the inadvertent detection of endometrial thickening in 13 women (out of 15 women with incidental findings), who were only investigated further if the women were symptomatic or had "particularly suspicious findings" (i.e., endometrial stripe >10 mm). The remaining two women with incidental findings had bladder abnormalities and were found to have significant pathology.

Finally, data are available from another prospective, randomized study in the United Kingdom. Menon and colleagues report the results of an initial screening round and 1-year followup. Of the 13,582 women who entered the study, 6,682 were randomly assigned to screening, 6,532 of whom underwent initial testing.[8] Women aged 50 years and older without active malignancy and without familial increased risk of ovarian cancer were eligible for inclusion. For the initial screening, CA-125 testing was performed, and for followup of initially abnormal values, an age-based algorithm compared subsequent values of CA-125 tests and determined the rate of change. For women classified as elevated risk (i.e., algorithm risk $\geq$1 in 5 after initial screening or followup), TVU was performed. TVU was performed at the central screening unit or at a collaborating center by a consultant radiologist or experienced ultrasonographer, with no mention of how many collaborating centers were involved. Further followup and surgery was performed by the woman's own general practice and specialists, and data were collected by medical record review.

Fewer than 1 percent of women in this screening study had surgery to investigate an abnormal screening test result (16 of 6,532), and in these 16 women, three invasive epithelial ovarian cancer cases were found, one metastatic recurrence of breast cancer and one borderline ovarian tumor. Of note, nearly 20 percent of the over 6,500 women who underwent the first screening were initially categorized as intermediate risk by the algorithm, and these women underwent up to five additional followup blood tests before being returned to the low risk pool. Of the women recalled for four or more tests, 6 percent (15 of 252) withdrew from the study and provided the disruption and stress resulting from repeat testing as the primary reason for their withdrawal.

These three studies offer quite different perspectives. The higher positive-screen rate in the Rufford study for both screening tests could reflect the fact that all women in that study had symptoms of some sort, and while none had cancer, it is possible that their symptoms were caused by some pathology that also caused one or both screening tests to be abnormal. The markedly lower surgical rate in both U.K. studies might be related to the different patient populations in the studies; that is, women from different countries at different levels of risk. It is also possible that variation in health care providers is a source of some of the difference; in the U.S. trial, patients' own physicians chose their management, as was also true in the Menon et al

study, while the Rufford et al trial provided specialized care and followup at a single referral center after any positive test. Variation among acceptable practice between countries could also play a role.

Emerging Issues and Research Gaps

Basic research is under way to study serum markers for detection of ovarian cancer and both serum and tissue markers for predicting disease progression. Recent research reports concerning serum markers include soluble tumor necrosis factor receptors,[9] which are associated with worse ovarian cancer outcomes, while overexpression of the p53 protein has been found to be associated with epithelial ovarian carcinoma more than low malignant potential tumors or benign neoplasms.[10] The main gap in our knowledge that is key to making the case for screening remains the uncertain ability to offer effective treatment of cancer at an early stage to improve the ultimate outcome.

There are two ongoing large trials that involve screening for ovarian cancer in average-risk women: the U.K. Collaborative Trial of Ovarian Cancer Screening, a randomized, controlled trial of 200,000 postmenopausal women, and the PLCO Cancer Screening Trial, which has enrolled 74,000 women in the United States.[11]

Conclusion

In summary, we found no substantial new evidence since 2004 on the benefits of screening for ovarian cancer. Some new information on the harms of screening is available, and confirms what was suspected in 2004 about the hazards of screening—that many women could be subjected to unnecessary surgery. Several large screening studies currently under way should be able to provide direct evidence on the benefits of screening ultrasonography or CA-125 testing in terms of mortality caused by ovarian cancer and other clinically relevant health outcomes.

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