Screening for Ovarian Cancer: Brief Evidence Update

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Background

In 1996, the USPSTF stated that routine screening for ovarian cancer by ultrasound, the measurement of serum tumor markers, or pelvic examination was not recommended (D recommendation).[1] There was insufficient evidence to recommend for or against the screening of asymptomatic women at increased risk for developing ovarian cancer (C recommendation). In addition, the USPSTF indicated that although there was no direct evidence from prospective studies that women with early-stage ovarian cancer detected through screening have lower mortality from ovarian cancer than do women with more advanced disease, indirect evidence supported this rationale. Available screening tests, however, were found to be inadequately sensitive/specific for screening and had not been adequately tested for this purpose.

Epidemiology

Ovarian cancer is the fifth leading cause of cancer death among women in the U.S., accounting for an estimated 23,400 new cases and 13,900 deaths in 2001.[3] Risk for ovarian cancer increases with age and peaks in the eighth decade.[3] The overall age-adjusted incidence rate is 16.8 cases per 100,000 (95% confidence interval [CI], 16.6–17.1) and the age-adjusted rate for women aged 50 and older is 44.4 per 100,000 (95% CI, 43.5–45.2).[4] Approximately 90% of malignant ovarian tumors are of epithelial origin.

The 5-year relative survival rate for all stages of ovarian cancer in the U.S. is 50%, but may improve to 95% for women whose disease is detected and treated at stage I.[3] However, up to 75% of women with ovarian cancer have non-localized disease at the time of diagnosis because early stages are often asymptomatic. Five-year relative survival rates for women with regional and distant disease are 79% and 28%, respectively.[3] Efforts to develop screening methods and strategies are focused on increasing the proportion of cases detected in early stages, particularly stage I.

A number of risk factors have been associated with ovarian cancer. The strongest associations related to reduced risk include oral contraceptive use (relative risk [RR] 0.66; 95% CI, 0.55–0.78) and any term pregnancy (RR 0.47; 95% CI, 0.4–0.56).[5] The strongest association with increased risk is family history. Existence of 1 first- or second-degree relative with ovarian cancer increases the RR to 3.1 (95% CI, 2.2–4.4); 2 or 3 relatives with ovarian cancer increases the RR to 4.6 (95% CI, 1.1–18.4).[6] Some studies suggest that postmenopausal

Systematic Evidence Reviews serve as the basis for U.S. Preventive Services Task Force (USPSTF) recommendations on clinical prevention topics. The USPSTF tailors the scope of these reviews to each topic. The USPSTF determined that a brief evidence update was needed to assist in updating its 1996 recommendations on screening for ovarian cancer.[1]

To assist the USPSTF, the Oregon Evidence-based Practice Center, under contract to the Agency for Healthcare Research and Quality (AHRQ), performed a targeted review of the literature published on this topic from 1995 to 2002. This brief evidence update and the updated recommendation statement[2] are available through the AHRQ Web site (www.preventiveservices.ahrq.gov) and in print through subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.* The subscription costs $60 and can be ordered through the AHRQ Publications Clearinghouse (call 1-800-358-9295, or e-mail ahrqpubs@ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

estrogen use is a risk factor for ovarian cancer,[7,8] while others do not.[9] It has not yet been determined how to use these risk factors in a screening strategy.

In some families, the pattern of cancers suggests the presence of a dominantly inherited gene (BRCA1, BRCA2). Carriers of the BRCA1 gene in such linkage families may have a risk of up to 60% for developing ovarian cancer by the age of 70, as well as an increased risk for breast cancer.[10] Carriers of the BRCA2 gene are at increased risk for ovarian, colorectal, endometrial, stomach, and possibly pancreatic cancer.[10] A growing literature focuses on the identification of women who carry these genes by genetic testing for the purposes of initiating measures to prevent ovarian and related cancers (ie, surveillance, prophylactic oophorectomy).

Current screening methods include transvaginal or transabdominal ultrasound scanning of the ovaries and measurement of the tumor-marker cancer antigen 125 (CA 125) in serum. Although several other tumor markers have been associated with ovarian cancer, they have not been widely tested for screening purposes. When used for screening, CA 125 measurement is usually followed by ultrasound scanning in women with abnormal levels. The definition of abnormal level varies with menopausal status. The presence of rising CA 125 levels obtained by serial measurements has also been used to indicate possible tumor activity. There are no universally accepted criteria for distinguishing between benign and malignant conditions on the basis of ultrasound findings. Several systems for classifying and scoring abnormalities have been described.[11–13] Women with persistently abnormal findings on these tests are referred for diagnostic abdominal surgery usually including oophorectomy. Treatment of diagnosed cancers includes surgery and chemotherapy or other adjuvant therapy for tumors that have extended beyond the ovaries.

Methods

In conjunction with a medical librarian, we conducted literature searches using MEDLINE® (January 1995–December 2002) (search terms are listed in the Appendix) and the Cochrane Controlled Trials Register (www.cochrane.org), yielding 685 abstracts. Additional articles were obtained by reviewing reference lists of pertinent studies, reviews, and editorials. We also reviewed results of a systematic review on screening for ovarian cancer by the Health Technology Assessment (HTA) program in the United Kingdom.[14] Studies were included if they addressed the key questions for the target population of asymptomatic women. Studies were excluded if the population was selected according to prior test results. Papers related to genetic testing were also excluded because they are beyond the scope of screening recommendations for the general population. This topic will be addressed in an upcoming recommendation from the USPSTF.

Analytic Framework

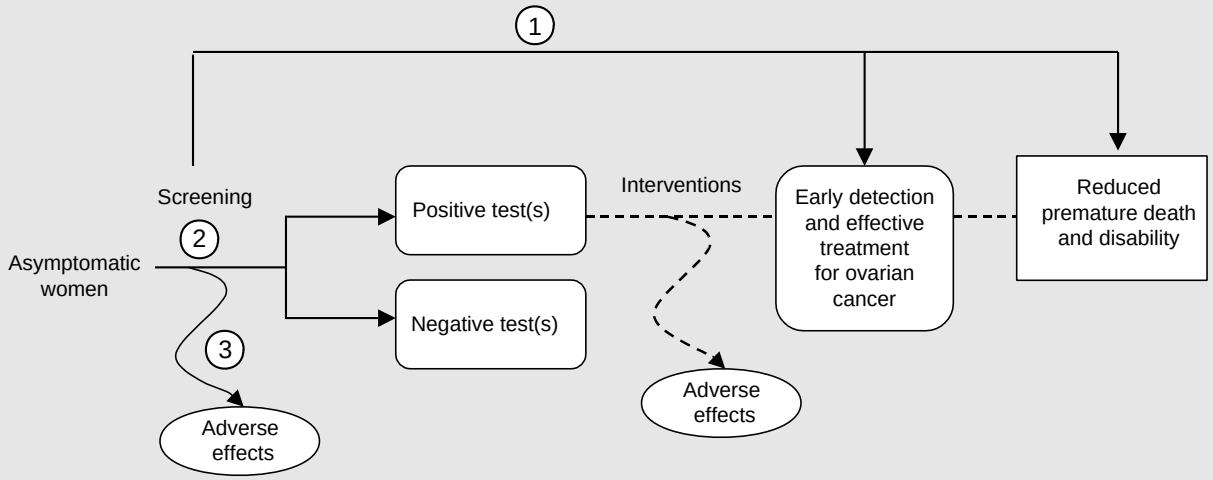
The analytic framework indicates the target population, interventions, and health outcome measures examined (Figure 1). This update will focus on studies of screening and performance of detection technologies available since the last USPSTF review. Numbered arrows in the figures correspond to the key questions considered, as listed below.

Key Questions and Results

1. Does screening for ovarian cancer among asymptomatic women result in early detection and, with effective treatment, reduce premature death and disability?

Screening studies with early detection outcomes. The HTA systematic review reported that both CA 125-based multimodal screening (CA 125 followed by ultrasound if CA 125 levels are high) and ultrasound screening alone can detect a higher proportion of ovarian cancers at stage I than the 25% currently observed in the U.K.[14] This report estimated that approximately 50% (95% CI, 23–77) of ovarian cancers are diagnosed at stage I in the 4 CA 125-based multimodal screening studies examined,[15–18] and approximately 75% (95% CI, 35–97) in the 8 ultrasound screening studies.[19–26] For women with a family history of ovarian cancer, 60% (95% CI, 32–84) are diagnosed at stage I based on

Figure 1. Screening for Ovarian Cancer Analytic Framework and Key Questions



Key Questions
Arrow 1: Does screening for ovarian cancer among asymptomatic women result in early detection and, with effective treatment, reduce premature death and disability?
Arrow 2: How well do screening tests or procedures identify women with ovarian cancer?
Arrow 3: What are the harms of screening?

8 studies using either of the techniques. However, the studies for which all of these estimates are based reported small numbers of cancer cases, varied in methods, and enrolled mostly self-selected women.

Three prospective studies of screening published after the systematic review are consistent with these findings. A 10-year study of 183,034 asymptomatic pre- and postmenopausal women in Japan, undergoing primary screening with transvaginal ultrasonography in a voluntary community screening program, reported that 58.8% of 85 ovarian cancers detected were stage I.[27] Another study of transvaginal ultrasonography screening in the U.S. enrolled over 14,000 asymptomatic women, including normal risk women aged 50 and older, and women with a family history of ovarian cancer aged 25 and older.[28] Women meeting criteria for abnormal sonograms were further evaluated by repeat scans. Those with persistently abnormal scans were referred for surgery. Approximately 65% of tumors in this study were stage I. A pilot randomized controlled trial (RCT) to determine feasibility of multimodal screening (CA 125 followed by ultrasound if CA 125 levels were high) was recently conducted in nearly 22,000 women in screening and control groups in the U.K.[29] Results indicated that 50% of cancers detected by screening, and 5% of those in the control group, were stage I.

Screening studies with mortality outcomes. No RCTs of screening for ovarian cancer in the general population with mortality outcomes have been completed, although some are currently in progress. These include the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS),[30] the European Randomized Trial of Ovarian Cancer Screening (ERTOCS),[30] and the NIH Prostate, Lung, Colon, Ovary (PLCO) trial in the U.S.[31,32]

The UKCTOCS is enrolling 200,000 postmenopausal women aged 50 to 74 recruited from community registers. These women are randomized in a 1:1:2 ratio to ultrasound screening, multimodal screening (sequential CA 125 tests followed by ultrasound in those testing positive), and a control group. Positive thresholds for CA 125

are calculated on the basis of age and level of change of CA 125 levels. Women will be tested annually 6 times, and follow-up will continue for 7 years using cancer registrations and postal questionnaires to obtain mortality outcomes. Additional endpoints include quality of life, health economics, morbidity, and compliance with screening.

The ERTOCS trial is recruiting women aged 50 to 64 from population registries or from breast cancer screening programs to total 30,000 in each intervention arm and 60,000 in the control group. The screening protocol includes transvaginal ultrasound at either 18- or 36-month intervals. Women are referred for repeat scans if ovarian volume is 3 or more multiples of the median for postmenopausal women or if a complicated or large ovarian cyst is present. The study may include a 10-year follow-up time using cancer registrations and death notifications for mortality outcomes.

The NIH PLCO trial has recruited women aged 55 to 74 by using primarily mass mailings for a total 38,000 women in each arm. The screening protocol includes transvaginal ultrasound annually for 4 years and CA 125 annually for 5 years. A control group receives usual care. A positive result on testing initiates a referral to the patients' own physicians for diagnosis.

2. How well do screening tests or procedures identify women with ovarian cancer?

The HTA review identified 16 prospective cohort studies of screening in asymptomatic, average-risk women that reported data on sensitivity and specificity of tests for women who underwent diagnostic surgery.[14,33] Findings indicated that the sensitivity of annual ultrasound screening was approximately 100%, with a false-positive result rate of approximately 1.2% to 2.5% based on 5 studies.[21,23–25,34] The addition of color Doppler imaging to ultrasound screening reduced the false-positive rate to 0.3% from 0.7%; however, results of studies were inconsistent.[23,35] The sensitivity of annual CA 125-based multimodal screening was estimated at 80%, with false-positive rates of 0.1% to 0.6% based on 3 studies.[15,16,18] All these estimates were based on small numbers of cancers, and studies varied in length of follow-up, although most did not extend longer than 1 year. Not enough data are available to determine the sensitivity and specificity of successive screening rounds.

3. What are the harms of screening?

Because of the low incidence of ovarian cancer in the general U.S. population, the positive predictive value (PPV) of screening is low. The HTA evidence review estimated that using annual ultrasound screening, only 0.6% of those recalled for abnormal results, and 3% undergoing surgery, have cancer.[14] The PPV for CA 125-based multimodal screening was estimated as 1% for initial recall and 15% for surgery.

An estimated 3% to 12% of screened women will be recalled for further testing and assessment, resulting in potential distress and anxiety to otherwise healthy women.[33] Approximately 0.5% to 1% of women will suffer a significant complication because of surgery, based on reports from published studies.[14]

Discussion

The HTA systematic review applied estimates from currently available studies to outcome tables to determine the potential benefits and harms of ovarian cancer screening. These calculations assumed an average annual incidence of ovarian cancer of 40 per 100,000 for women aged 50 to 64 and a 40% reduction in mortality with screening. Two approaches were evaluated: one using biannual transvaginal ultrasound (assuming 7% of women recalled for abnormal findings and 1.3% false-positive results at diagnostic surgery) and another using annual CA 125 (assuming 3% recall and 0.2% false-positive results). Results are illustrated in Table 1. A sensitivity analysis that considered higher risk women using bi-annual transvaginal ultrasounds indicated improved predictive value (Table 2).

Available evidence indicates that screening asymptomatic, average-risk women with ultrasound or with CA 125 tests followed by ultrasound, if levels are high, can detect ovarian cancer at an earlier stage than it would be detected in an unscreened population. The sensitivity of ultrasound screening after 1 year of follow-up approaches 100% and CA

Table 1. Annual Outcomes of Ovarian Cancer Screening in a Hypothetical Cohort of 10,000 Women Aged 50 to 64 Assuming 40% Mortality Reduction and an Annual Incidence of 40 per 100,000*

Women Screened and Predictive Value of Interventions	CA 125	Transvaginal Ultrasound
Number of women participating in screening program	10,000	10,000
Screening interval	Annual	Every 2 years
Number of screening tests carried out per year	10,000	5,000
Number of women recalled for further assessment per year who do not have primary ovarian cancer	300 (3% of screens)	350 (7% of screens)
Number of women undergoing surgery per year who do not have primary ovarian cancer	20 (0.2% of screens)	65 (1.3% of screens)
Maximum number of cancers detected by screening per year (if 100% sensitivity)	4	4
Number of additional 5-year survivors per year	1.5	1.5
Predictive value of recall (if 100% sensitivity)	1.3%	1.1%
Predictive value of diagnostic surgery (if 100% sensitivity)	17%	5.8%

*Adapted from Bell et al, 1998.[33]

Table 2. Annual Outcomes of Ovarian Cancer Screening in a Hypothetical Cohort of 10,000 Women Aged 50 to 64 at Higher Risk Assuming 40% Mortality Reduction and Using Bi-annual Transvaginal Ultrasound*

Women Screened and Predictive Value of Interventions	Three Times Risk (1 in 830 per Year)	Ten Times Risk (1 in 250 per Year)
Number of women participating in screening program	10,000	10,000
Screening interval	Every 2 years	Every 2 years
Number of screening tests carried out per year	5,000	5,000
Number of women recalled for further assessment per year who do not have primary ovarian cancer	350 (7% of screens)	350 (7% of screens)
Number of women undergoing surgery per year who do not have primary ovarian cancer	65 (1.3% of screens)	65 (1.3% of screens)
Maximum number of cancers detected by screening per year (if 100% sensitivity)	12	40
Number of additional 5-year survivors per year	4.8	16
Predictive value of recall (if 100% sensitivity)	3.3%	10.3%
Predictive value of diagnostic surgery (if 100% sensitivity)	16%	38.1%

*Adapted from Bell et al, 1998.[33]

125-based screening, 80%; however, these estimates are based on limited data. Although specificity for either strategy is high, the predictive value of a positive test is low because of the low prevalence of ovarian cancer in the general population. The studies in which these estimates are based were not RCTs of screening, did not report mortality outcomes, had short lengths of follow-up, reported few cancer cases, and often included self-selected volunteers. Important biases limit the interpretation of the results of these studies. Large RCTs of screening with mortality outcomes are currently in progress and will provide more definitive evidence of the benefits and harms of ovarian cancer screening.

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Appendix

MEDLINE® Search Strategy	
Dates include January 1995–December 2002	
1	exp Ovarian Neoplasms/ or ovarian cancer.mp.
2	exp Mass Screening/ or screening.mp.
3	exp Physical Examination/ or pelvic exam$.mp.
4	exp Vaginal Smears/ or pap smear.mp.
5	exp Tumor Markers, Biological/ or tumor markers.mp.
6	ultrasound imaging.mp. or exp Ultrasonography/
7	2 or 3 or 4 or 5 or 6
8	1 and 7
9	limit 8 to yr=1995–2002
10	limit 9 to (human and English language)
11	limit 10 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial)
12	exp clinical trials/ or clinical trial$.mp.
13	exp Epidemiologic Studies/ or epidemiologic studies.mp.
14	cohort stud$.mp.
15	12 or 13 or 14
16	10 and 15
17	11 or 16
18	from 17 keep 1–600

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