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Screening for Ovarian Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Ovarian cancer is relatively rare but the fifth-leading cause of cancer mortality among United States women.

OBJECTIVE To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk women to inform the United States Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, Cochrane Collaboration Registry of Controlled Trials; studies published in English from January 1, 2003, through January 31, 2017; ongoing surveillance in targeted publications through November 22, 2017.

STUDY SELECTION Randomized clinical trials of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal ultrasound, cancer antigen 125 (CA-125) testing, or their combination. Comparators were usual care or no screening.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction by 2 reviewers. Meta-analytic pooling of results was not conducted because of the small number of studies and heterogeneity of interventions.

MAIN OUTCOMES AND MEASURES Ovarian cancer mortality, false-positive screening results and surgery, surgical complications, and psychological effects of screening.

RESULTS Four trials (N = 293 587) were included; of these, 3 (n = 293 038) assessed ovarian cancer mortality, and 1 (n = 549) reported only on psychological outcomes. Evaluated screening interventions included transvaginal ultrasound alone, transvaginal ultrasound plus CA-125 testing, and CA-125 testing alone. Test positivity for CA-125 was defined by a fixed serum level cutpoint or by a proprietary risk algorithm based on CA-125 level, change in CA-125 level over time, and age (risk of ovarian cancer algorithm [ROCA]). No trial found a significant difference in ovarian cancer mortality with screening. In the 2 large screening trials (PLCO and UKCTOCS, n = 271 103), there was not a statistically significant difference in complete intention-to-screen analyses of ovarian, fallopian, and peritoneal cancer cases associated with screening (PLCO: rate ratio, 1.18 [95% CI, 0.82-1.71]; UKCTOCS: hazard ratio [HR], 0.91 [95% CI, 0.76-1.09] for transvaginal ultrasound and HR, 0.89 [95% CI, 0.74-1.08] for CA-125 ROCA). Within these 2 trials, screening led to surgery for suspected ovarian cancer in 1% of women without cancer for CA-125 ROCA and in 3% for transvaginal ultrasound with or without CA-125 screening, with major complications occurring among 3% to 15% of surgery. Evidence on psychological harms was limited but nonsignificant except in the case of repeat follow-up scans and tests, which increased the risk of psychological morbidity in a subsample of UKCTOCS participants based on the General Health Questionnaire 12 (score ≥4) (odds ratio, 1.28 [95% CI, 1.18-1.39]).

CONCLUSIONS AND RELEVANCE In randomized trials conducted among average-risk, asymptomatic women, ovarian cancer mortality did not significantly differ between screened women and those with no screening or in usual care. Screening harms included surgery (with major surgical complications) in women found to not have cancer. Further research is needed to identify effective approaches for reducing ovarian cancer incidence and mortality.

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Although ovarian cancer is uncommon, it is the fifth-leading cause of cancer mortality among US women. Based on data from 2010-2014, the estimated annual incidence rate was 11.4 per 100 000 and the mortality rate was 7.4 per 100 000, with a projected 14 080 deaths from ovarian cancer in 2017.[1,2] More than 60% of cases are diagnosed after the cancer has metastasized.[2] Screening trials have shown no effect on mortality and have documented harms; positive test results from screening asymptomatic women often reveal benign pelvic conditions or normal ovaries on surgical investigation, and cancer cases are often missed with screening.[3-5] In 2012, the US Preventive Services Task Force (USPSTF) concluded that there was at least moderate certainty that the harms of screening for ovarian cancer outweighed the benefits, and it issued a D grade recommendation against screening in asymptomatic women. The current review was undertaken to update the evidence on population-based screening for ovarian cancer for an updated recommendation on this topic.[4]

Methods

Scope of Review

This evidence review addresses 2 key questions (KQs) related to benefits and harms of screening for ovarian cancer in asymptomatic women (**Figure 1**). Methodological details regarding search strategies, detailed study inclusion criteria, quality assessment, excluded studies, and description of data analyses, as well as detailed results, are publicly available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/ovarian-cancer-screening1.

Data Sources and Searches

A search of MEDLINE, PubMed publisher-supplied records, and the Cochrane Collaboration Registry of Controlled Trials for studies published between January 2003 and January 2017 built on a previous search conducted on behalf of the USPSTF (eMethods in the Supplement).[7] Studies also were identified from previous reviews, meta-analyses, and reference lists.[5,7-10] ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. Since January 2017, ongoing surveillance to identify new studies that might affect the review conclusions or interpretation of the evidence was conducted using article alerts and targeted searches of journals with high impact factors. The last surveillance, conducted on November 22, 2017, identified an additional publication reporting secondary analyses of one of the included trials.[11]

Study Selection

Two reviewers independently reviewed titles, abstracts, and full article text to identify studies meeting predetermined review inclusion and exclusion criteria (eTable 1 in the Supplement). Discrepancies were resolved by discussion. Randomized clinical trials of screening compared with no screening or usual care comparisons that enrolled asymptomatic, average-risk women 45 years and older were included. Trials focused on screening explicitly among high-risk populations (eg, *BRCA* mutation carriers, individuals with first-degree relatives with ovarian cancer), and those addressing only the accuracy of screening or cancer detection rates without reporting morbidity, mortality, or quality-of-life data, were not included.

Data Extraction and Quality Assessment

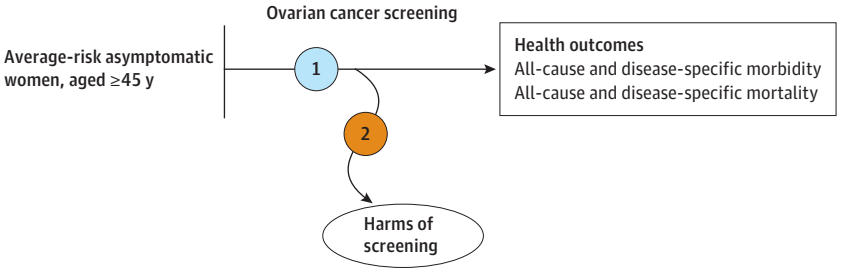
Two reviewers independently assessed the methodological quality of all eligible studies, using criteria outlined by the USPSTF (eTable 2 in the Supplement),[12] and resolved discordant ratings through discussion. Good-quality randomized clinical trials had adequate randomization procedures and allocation concealment, blinded outcome assessment, reliable outcome measures, similar baseline characteristics between groups, and low attrition. Good-quality trials also used intention-to-screen analysis and reported diagnostic criteria for outcome ascertainment. Fair-quality studies were assessed as not meeting all of the quality criteria but did not have critical limitations that could invalidate study findings. Trials were rated poor quality if attrition was greater than 40% or differed between groups by 20% or if there were other study design or implementation flaws that would seriously undermine internal validity.

Data Synthesis and Analysis

One reviewer abstracted data into standard evidence tables, and the second reviewer checked them for accuracy. Descriptive synthesis was conducted, with results reported and discussed by screening strategy. Meta-analytic pooling of results was not conducted because of the small number of studies and heterogeneity of interventions. Some outcomes were calculated from raw data reported in study publications to adhere to task force priorities or to facilitate comparability across trials and thus may differ from the findings highlighted in the main results of the original publications. As per definitions endorsed by the 2014 World Health Organization and the Fédération Internationale de Gynécologie Obstétrique, ovarian cancer includes ovarian, tubal, and peritoneal cancers.[13,14] This definition recognizes that the clinical presentation and treatment of peritoneal cancers is not readily distinguished from advanced ovarian or fallopian tube cancers; pathological distinctions are also challenging.[15-17] Cancer cases were abstracted or calculated using this definition when possible, even if it was not the primary trial outcome reported. Screening false-positive rates were calculated as the percentage of women not diagnosed with ovarian cancer who experienced a positive screening result that led to follow-up testing. False-positive surgery rates were calculated as the percentage of women without an ovarian cancer diagnosis who were referred to surgery for investigation of suspected ovarian cancer based on positive screening and follow-up test results. Because each definition provides different insights, false-positive rates based on both definitions were calculated for all included studies that reported the pertinent data.

When multiple statistical tests were presented in publications, the prespecified statistical analyses from trial protocols were prioritized, as were complete intention-to-screen analyses and clinically meaningful mortality outcomes for ovarian cancer as defined above.[18] The strength of the overall body of evidence for each key question was graded as high, moderate, low, or insufficient based on established methods[19] and addressed the consistency, precision, and limitations of the body of evidence related to each outcome. For more details on review methods, see the full report.

Figure 1. Analytic Framework and Key Questions



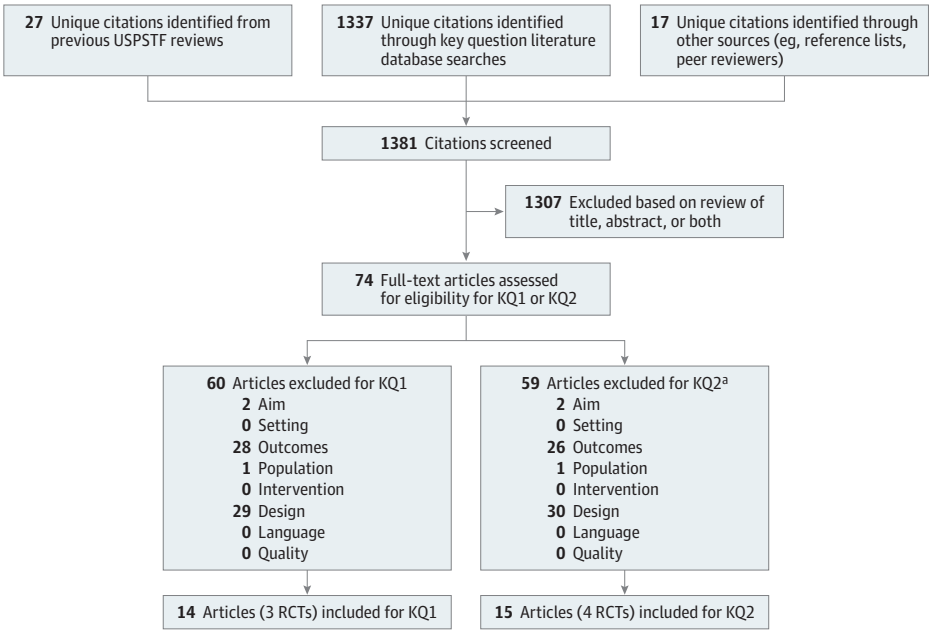
Key questions

1. Does screening for ovarian cancer in asymptomatic women using single tests or combined algorithms (such as, but not limited to, cancer antigen 125 [CA-125] and ultrasound) reduce all-cause or disease-specific morbidity and mortality?

2. What are the harms of screening for ovarian cancer, including harms of the screening test and of diagnostic evaluation?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for further details.[6]

Figure 2. Literature Search Flow Diagram



KQ indicates key question; RCT, randomized clinical trial; USPSTF, US Preventive Services Task Force.

[a] Reasons for exclusion: Aim: Study aim was not relevant. Setting: Study was not conducted in a country relevant to United States practice or not conducted in, recruited from, or feasible for primary care or a health system. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Population: Study was not conducted in an included population. Intervention: Intervention was out of scope. Design: Study did not use an included design. Language: Publication not in English. Quality: Study was poor quality.

Results

A total of 1381 titles and abstracts and 74 articles were reviewed. After full text review and critical appraisal, 4 trials (N = 293 587) in 17 publications were included (**Figure 2**).[20-36] Three trials reported health outcomes (KQ1), and all 4 trials reported potential harms of screening (KQ2) (**Table 1**). Two of the trials were conducted in the United States[21,29] and 2 in the United Kingdom.[31,33] The UK Pilot and UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) were limited to postmenopausal women 45 years and older and 50 to 74 years[31,33]; the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial included women aged 55 to 74 years[21]; and the Quality of life, Education, and Screening Trial (QUEST) included women 30 years and older.[29] Data on false-positive rates, surgical harms, and psychological harms of screening were obtained from the 3 good-quality trials[21,25,31,33] and the fair-quality QUEST[29] trial (n = 549).

The largest (n = 202 546), most recent trial is UKCTOCS, which enrolled participants through 13 National Health Service centers in England, Wales, and Northern Ireland. The smaller (n = 21 935) UK Pilot trial, conducted by the same research group in preparation for UKCTOCS,[33] recruited women who had participated in a previous ovarian cancer screening study.[32] The PLCO trial (n = 68 557) was conducted at 10 clinical screening centers in the United States.[21,38]

Table 1. Characteristics of All Included Trials

Source	Quality[a]	Study Dates	No. Randomized	No. Analyzed	White, %	Family History of Breast or Ovarian Cancer, %	Enrollment and Recruitment Source	Inclusion and Exclusion Criteria	Key Outcomes Reported[b]
UKCTOCS,[31] 2016 United Kingdom	Good	2001-2004	202 638	202 546	96	1.6 (ovarian) 6.4 (breast)	National Health Service catchments of 13 regional centers in Wales, England, and Northern Ireland; women recruited from 27 primary care service groups in the regions	Inclusion: Postmenopausal, aged 50-74 y Exclusion: Self-reported history of bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, active nonovarian malignancy	KQ1: Ovarian cancer (ovarian, fallopian tube, and peritoneal cancer) incidence and mortality KQ2: Screening false-positive rates, surgery, and surgical complications
PLCO,[21] 2011 United States	Good	1993-2010[c]	78 216	68 557[d]	88	17.4	Community volunteers from the catchment areas of 10 screening centers	Inclusion: Aged 55-74 y Exclusion: Previous bilateral oophorectomy; history of lung, colorectal, or ovarian cancer; current treatment for cancer other than nonmelanoma skin cancer; colonoscopy, sigmoidoscopy, or barium enema in past 3 y; previous surgical removal of lung or entire colon; participation in other screening trial[e]	KQ1: Ovarian cancer (ovarian, fallopian tube, and peritoneal cancer) incidence and mortality KQ2: Screening false-positive rates, surgery, and surgical complications
QUEST,[29] 2007 United States	Fair	NR	592	549	95	17.1	Population volunteers, physician referral	Inclusion: aged ≥30 y Exclusion: High risk of ovarian cancer[f]; cancer diagnosis in past year; plans to become pregnant in the following 2 y	KQ2: Psychological harms of screening program participation
UK Pilot,[33] 1999 United Kingdom	Good	1989-1998	21 955	21 935	95	NR	Community volunteers and postal invitations to 40 primary care practices in England, Scotland, and Wales	Inclusion: Postmenopausal, ≥45 y old Exclusion: History of bilateral oophorectomy, ovarian cancer, or any active malignancy	KQ1: Ovarian cancer (ovarian, fallopian tube cancer) incidence and mortality KQ2: Screening false-positive rates and surgical complications

Abbreviations: NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; QUEST, Quality of Life, Education, and Screening Trial; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

[a] Methodological quality of each study using predefined criteria developed by the US Preventive Services Task Force.[12]

[b] Ovarian cancer was defined according to the 2014 World Health Organization and Fédération Internationale de Gynécologie Obstétrique definitions, which include ovarian, tubal, and peritoneal cancers.[13,14] Cancer cases were abstracted or calculated using this definition when possible, even if cancer was not the primary outcome reported in the trial. The PLCO[21] and UKCTOCS[31] trials reported cases of ovarian, fallopian, and primary peritoneal cancer cases. Data from the earlier UK Pilot trial did not report cases of peritoneal cancer[33]; therefore, those results are limited to primary cancer of the ovary and fallopian tubes.

[c] Additional mortality data published through 2012.[35]

[d] Analysis excluded 9659 women because of oophorectomy before trial entry (included in number randomized because they were screened for other cancers in the PLCO trial).

[e] Exclusion based on colorectal cancer screening began 1995. Trial initially excluded women with previous oophorectomy (dropped in 1996) and current tamoxifen use (dropped in 1999).

[f] High risk of ovarian cancer: reported family history predicted at least a 10% probability of a germline mutation in the *BRCA1* or *BRCA2* genes or Amsterdam criteria for hereditary nonpolyposis colorectal cancer syndrome.[37]

Table 2. Screening Protocols for Trials Addressing Ovarian Cancer Mortality (Key Question 1)[a]

Source	Screening Intervention	Abnormal Test Result Definitions	Follow-up Protocol for Screen-Positive Women	Comparison Group	Screening Frequency	Maximum No. of Screening Rounds	Follow-up, Median (Range), y	Ovarian Cancer Cases During Follow-up, %[b]
UKCTOCS,[31] 2016	Group 1: CA-125 testing with ROCA algorithm used to determine risk-based protocol for follow-up[c]	Intermediate risk (risk ≥1/1818); elevated risk (risk ≥1/500)[d]	Clinical assessment and surgical investigation conducted by trial clinicians according to a specified protocol depending on screening result	No screening	Annual	11[e]	11.1 (0-13.6)	1323 (0.65) (group 1 and group 2)
	Group 2: TVU	One or both ovaries with complex morphology, simple cysts >60 cm^3, or ascites	Clinical assessment and surgical investigation conducted by trial clinicians	No screening	Annual	11	11.1 (0-13.6)	
PLCO,[21] 2011	TVU and CA-125[f]	CA-125: ≥35 U/mL TVU: Ovarian volume >10 cm^3; cyst volume >10 cm^3; any solid area or papillary projection extending into the cavity of a cystic ovarian tumor of any size; or any mixed (solid and cystic) component within a cystic ovarian tumor	Notification of patients and their primary care physicians; follow-up through community care	Standard community care	Annual	CA-125: 6 TVU: 4	12.4 (NR)	388 (0.57)
UK Pilot,[33] 1999	CA-125 testing; follow-up included ultrasound for elevated CA-125 levels[g]	CA-125 ≥30 U/mL	Referral through family physician to a gynecologist for surgical investigation	No screening	Annual	3[h]	NR (0-8)	36 (0.16)

Abbreviations: CA-125, cancer antigen 125; IQR, interquartile range; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ROCA, risk of ovarian cancer algorithm; TVU, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

[a] All studies were good quality.

[b] No evidence of a difference in incidence of ovarian cancer between the study groups.

[c] Follow-up included repeat CA-125 test (intermediate risk) or repeat CA-125 and TVU (elevated risk) based on ROCA.

[d] CA-125 levels were changed in 2005 to maintain the percentage in each risk level (intermediate, ≥1/3500; elevated, ≥1/1000); 84.6% of screens were classified using pre-2005 cutoffs.

[e] Extended from original protocol of 6 screening rounds based on interim analysis.

[f] Annual bimanual clinical examination of the ovaries discontinued in 1998 because no cases were identified solely with this screening test.

[g] During the first screen, ultrasonography was performed transabdominally. Transvaginal ultrasonography was used in the second and third screens.

[h] All women in this trial (including the control group) had undergone a previous round of screening approximately 10 years prior.

The PLCO[21] and UKCTOCS[31] trials reported cases of ovarian, fallopian, and primary peritoneal cancer. Data from the earlier UK Pilot trial did not report cases of peritoneal cancer[33]; therefore, those results are limited to primary cancer of the ovary and fallopian tubes.

Benefits of Screening

Key Question 1. Does screening for ovarian cancer in asymptomatic women using single tests or combined algorithms (such as, but not limited to, cancer antigen 125 [CA-125] and ultrasound) reduce all-cause or disease-specific morbidity and mortality?

Three good-quality trials (n = 293 038) met the inclusion criteria for KQ1 (Table 1).

In the UKCTOCS and UK Pilot trials, the racial or ethnic composition of the study population was more than 95% white,[31,33] and in the PLCO trial 88% of women were white and non-Hispanic. In the UKCTOCS trial, women considered at "high risk" of familial ovarian cancer were explicitly excluded, but 1.6% of women reported maternal history of ovarian cancer and 6.4% a maternal history of breast cancer. In the PLCO trial,[21] 17% of women reported any family history of breast or ovarian cancer.

All 3 trials evaluated annual screening for ovarian cancer with CA-125 testing, transvaginal ultrasound, or both (**Table 2**). The UKCTOCS trial had 2 intervention groups and a no-screening control group (randomized 1:1:2, respectively). Women were originally randomized to receive annual screening for 6 years, but the protocol was modified to extend screening. Women randomized to the intervention group received 7 to 11 rounds of annual screening using CA-125 serum testing (with triage and follow-up determined by the risk of ovarian cancer algorithm [ROCA])[39,40] or yearly transvaginal ultrasound testing with a median of 11.1 years of follow-up.[31] The CA-125 ROCA screening group was described as multimodal screening in the UKCTOCS trial publications and included a standard protocol for all follow-up testing. The ROCA is more complex than single-cutpoint CA-125 testing because it incorporates changes in CA-125 level over time for individual women.

The UK Pilot[33] trial compared 3 rounds of annual CA-125 screening tests having a fixed cutpoint (≥30 U/mL) with no screening over 8 years of follow-up.[33]

Women in the screening intervention group of the PLCO trial received both CA-125 testing with a fixed cutpoint (≥35 U/mL) and

Table 3. Effects of Ovarian Cancer Screening on Ovarian Cancer Mortality (Key Question 1)[a,b]

Source	Screening Method	No. Analyzed		Ovarian Cancer Deaths, No. (%)		Ovarian Cancer Mortality per 10 000 Person-Years		Between-Group Difference in Mortality
		Screening Group	Control Group	Intervention	Control	Intervention	Control	
UKCTOCS,[31] 2016	CA-125 ROCA	50 624	101 299	160 (0.32)	358 (0.35)	2.9	3.3	HR, 0.89 (95% CI, 0.74-1.08); P = .23[c]
	TVU	50 623	101 299	163 (0.32)	358 (0.35)	3.0	3.3	HR, 0.91 (95% CI, 0.76-1.09); P = .31[c]
PLCO,[21] 2011	CA-125 + TVU	34 253	34 304	118 (0.34)	100 (0.29)	3.1	2.6	Rate ratio, 1.18 (95% CI, 0.82-1.71); P = NR[d]
UK Pilot,[33] 1999[e]	CA-125	10 958	10 977	9 (0.08)	18 (0.16)	NR	NR	Relative risk, 0.50 (95% CI, 0.22-1.11); P = .08[f]

Abbreviations: CA-125, cancer antigen 125; HR, hazard ratio; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; TVU, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

[a] Includes ovarian, fallopian, and primary peritoneal cancers.

[b] All studies were good quality.

[c] Cox model.

[d] Sequentially adjusted.

[e] Does not include peritoneal cancer.

[f] Calculated (article reports relative risk calculated in in terms of increased relative risk).

ultrasonography.[20,21] Bimanual palpation of the ovaries was also included in the screening intervention during the first 4 years of study enrollment but was discontinued because no cancers were identified only on the basis of this examination.[41] A protocol modification also extended screening to a maximum of 6 screening rounds (4 with CA-125 and transvaginal ultrasound, 2 with CA-125 alone), with a median of 12.4 years of follow-up.

Overall, screening adherence was high, follow-up rates were variable but balanced, and contamination across groups was minimal. Ovarian cancer was diagnosed in 0.6% of women (388 cases) in the PLCO trial, 0.7% of women (1323 cases) in the UKCTOCS trial, and 0.2% of women (36 cases) in the UK Pilot trial. Across all trials, incidence did not differ by study group.

CA-125 Screening

In the UKCTOCS trial, ovarian cancer mortality (including fallopian tube and peritoneal cancer) with the CA-125 ROCA screening program was similar in the intervention and control groups (0.32% for intervention vs 0.35% for control), and in survival analysis there were 2.9 ovarian cancer deaths per 10 000 person-years in the intervention group and 3.3 ovarian cancer deaths per 10 000 person-years in the control group. This difference was not statistically significant (hazard ratio, 0.89 [95% CI, 0.74-1.08])[31] (**Table 3**). In the smaller UK Pilot[33] trial (n = 21 935), there were 9 ovarian cancer (peritoneal cancer not reported) deaths in the intervention group (0.08%) and 18 in the no-screening comparison group (0.16%); the difference was not statistically significant (relative risk , 0.50 [95% CI, 0.22-1.11]). A statistically significant difference in survival between women with index cancers in the intervention and control groups was observed when computed from the date of randomization (median, 72.9 months for intervention group vs 41.8 months for control group; P = .01). This finding was based on a small number of events, and survival in the control group was noted by the study authors as being "unexpectedly poor," with only 2 of 20 women who developed an index cancer surviving.

Transvaginal Ultrasound Screening

In the UKCTOCS trial,[31] transvaginal ultrasound screening did not reduce ovarian cancer mortality compared with no screening (0.32% for intervention group vs 0.35% for control group) (Table 3). In survival analyses, ovarian cancer mortality was 3.0 per 10 000 person-years in the intervention group and 3.3 per 10 000 person-years in the comparison group (hazard ratio, 0.91 [95% CI, 0.76-1.09]).[31]

Combined CA-125 and Transvaginal Ultrasound Screening

The incidence of ovarian cancer mortality in the PLCO trial[21] was 3.1 per 10 000 person-years in the intervention group and 2.6 per 10 000 person-years in the usual care comparison group (Table 3). There were 118 deaths in the intervention group (0.34%) and 100 deaths in the control group (0.29%), a statistically nonsignificant difference (rate ratio, 1.18 [95% CI, 0.82-1.71]). Survival with ovarian cancer did not differ significantly between study groups.[21]

Harms of Screening

Key Question 2. What are the harms of screening for ovarian cancer, including harms of the screening test and of diagnostic evaluation?

Evidence on false-positive rates and surgical harms of screening were included from the 3 trials[21,31,33] included for KQ1 (**Table 4**).

CA-125 Screening

Across all incidence rounds (ranging from 2 to 11) of the UKCTOCS trial, 44.2% (20 340/46 067) of women without cancer screened in the CA-125 ROCA group had at least 1 false-positive test result, meaning that at least 1 of their annual CA-125 screening measurements generated an elevated-risk ROCA result requiring further protocol-defined follow-up.[34] This protocol-defined follow-up included retesting with CA-125 in 6 months, clinical examinations depending on the ROCA risk level, or both. Approximately 1% of women (n = 488) screened with the CA-125 ROCA strategy underwent surgery and did not have cancer found.[31] Major complications occurred in 3.1% of these operations (15/488), including infection, injury to hollow viscus, anesthetic complications, and cardiovascular and pulmonary events.[31]

Across 3 rounds of the UK Pilot trial, 4.2% (462/10 942) of women without cancer screened with CA-125 received a false-positive test result, and 0.2% eventually underwent surgery.[33] No surgical complications were reported in the UK Pilot trial.[33] The CA-125 screening tests resulted in minor complications (eg, fainting or bruising from blood draws), ranging from 0.86 in the UKCTOCS trial to 58.3 per 10 000 women in the PLCO trial.[21,31]

Table 4. False-Positive and Surgical Harms Reported in Ovarian Cancer Screening Trials (Key Question 2)[a]

Source	Quality[b]	False-Positive Screening Rate Across Entire Program, No. With False-Positive Screen/ No. Without Cancer (%)[c]	Screening Test Complications	False-Positive Surgery, No. Undergoing Surgery/ No. Without Cancer (%)	Women Without Cancer With Surgical Complications, No. With Complication/ No. With False-Positive Surgery (%)[d]
UKCTOCS, 2016[22,31,34] (CA-125 ROCA)	Good	20 340/46 067 (44.2) across 2-11 rounds of screening[e]	0.86 per 10 000 screens[f]	488/50 270 (0.97)	15/488 (3.07)[g]
UKCTOCS, 2016[22,31] (TVU)	Good	NR[h]	1.86 per 10 000 screens[i]	1634/50 299 (3.25)	57/1634 (3.49)[j]
PLCO, 2011[20,21,27]	Good	3285/34 041 (9.6) across 1-6 rounds of screening	CA-125: 58.3 per 10 000 women[k] TVU: 3.3 per 10 000 women[k]	1080/34 041 (3.17)	163/1080 (15.09)[l]
UK Pilot, 1999[33]	Good	462/10 942 (4.2) across 1-3 rounds of screening[m]	NR	23/10 942 (0.2)[m]	0
QUEST, 2007[29]	Fair	NA	NA	NA	NA

Abbreviations: CA-125, cancer antigen 125; NA, not applicable; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; TVU, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

[a] Includes ovarian, fallopian, and primary peritoneal cancers.

[b] Methodological quality of each study using predefined criteria developed by the US Preventive Services Task Force.[12.]

[c] Patient experience of first positive screening test result leading to additional triage or follow-up (including repeated testing because of unsatisfactory results).

[d] Among women with false-positive results (benign findings) who underwent surgery.

[e] The false-positive rate from the baseline screening round was 9.0% (4513/50 031). False-positives from baseline screening could not be combined with rates from screening rounds 2 to 11 because of differences in denominators. Cumulative data reported for women screened in rounds 2 to 11 were based on a denominator of women who continued screening after the first round.

[f] Includes bruising (13), pain (8), hematoma (3), fainting (1), cystitis/infection (1), other (4).

[g] Includes anesthetic complications (1), injury to hollow viscus (2 gastrointestinal, 1 bladder), hemorrhage (2), deep vein thrombosis (1), bowel obstruction (4), wound breakdown (1), significant ileus (1), uterine perforation (1), infection (1).

[h] Data reported only for prevalence round: 11.9% (5734/48 177).

[i] Includes pain (20), cystitis or infection (11), discomfort (5), bruising (2), fainting (1), other (22).

[j] Includes injury to hollow viscus (4 gastrointestinal, 3 bladder, 1 ureter), hemorrhage (11), anesthetic complication or myocardial infarction (3), hernia (6), deep vein thrombosis or pulmonary embolism (3), wound breakdown (6), bowel obstruction (4), wound or supravaginal hematoma (4), infection (6), pain with readmission or further operation (3).

[k] Minor complications (eg, fainting, bruising).

[l] Total of 222 complications in 163 patients. Includes infection (89), direct surgical harms (63), cardiovascular or pulmonary events (31), other (39).

[m] Does not include peritoneal cancers.

Transvaginal Ultrasound Screening

The number of women receiving a false-positive test result after transvaginal ultrasound testing over the course of all screening rounds of the UKCTOCS trial was not reported; however, for the initial round of screening a false-positive rate of 11.9% was reported.[22] Across the trial, 3.2% (1634/50 299) of women assigned to the UKCTOCS transvaginal ultrasound screening intervention underwent surgery and did not have cancer found. Major complications were reported for 3.5% of the operations, including infection, wound breakdown, anesthetic complication or myocardial infarction, deep vein thrombosis or pulmonary embolism, and injury to hollow viscus.[31] The screening tests resulted in minor complications (eg, pain, discomfort, infection, bruising), ranging from 1.86 per 10 000 women in the UKCTOCS trial to 3.3 per 10 000 women in the PLCO trial.[21,31]

Combined CA-125 and Transvaginal Ultrasound Screening

Across all rounds of screening (ranging from 1 to 6) in the PLCO trial, 9.6% (3285/34 041) of the women not found to have cancer received at least 1 positive screening result from CA-125 or transvaginal ultrasound testing. After additional follow-up in their usual care settings, 3.2% (1080/34 041) of women in the trial who did not have cancer underwent diagnostic surgery. Major complications occurred in 15.1% of these operations, including infection, direct surgical harms, cardiovascular or pulmonary events, and other unspecified adverse events.[21]

Psychological Outcomes

A study of the psychological morbidity associated with ovarian cancer screening was undertaken within the UKCTOCS trial[25] using an annual survey of a random sample of women drawn at baseline from each trial group (n = 1339) and surveys of all women in the screening groups who were recalled for follow-up testing (eTable 3 in the Supplement). No statistically significant differences in anxiety or risk of psychological morbidity were observed between the control and intervention groups in the random sample. In the analysis of women with recall screening events, there was a small, though statistically significant, effect of repeat screening on anxiety ($P < .01$) and an increased risk of psychological morbidity among women recalled for higher-level screening (12-Item General Health Questionnaire score $\geq$4, adjusted odds ratio, 1.28 [95% CI, 1.18-1.39]).[25] The small QUEST trial (n = 549) similarly found a higher level of cancer worry among women who had experienced any abnormal test results.[29]

Discussion

A summary of the evidence for this review is reported in **Table 5**. Since the previous review of this topic for the USPSTF, ovarian cancer mortality findings were published from the largest trial to date, the UKCTOCS trial. Evidence from 2 large trials in the United States and the United Kingdom among asymptomatic average-risk women does not indicate that screening reduces ovarian cancer mortality. The smaller UK Pilot trial was designed to assess feasibility and performance of screening and was not powered to test mortality differences. The UKCTOCS trial assessed a proprietary screening and follow-up intervention that led to fewer women without cancer undergoing surgery and experiencing complications in comparison to the PLCO trial. Nevertheless, in both trials the operations and complications occurred in the absence of a mortality benefit for the screened population.

Trial results from the complete intention-to-treat analysis of ovarian cancer mortality defined according to clinically relevant international standards are applicable to the implementation of a screening program and its cumulative effects.[42,43] Both of the large trials also provided additional analyses to explore effects and generate hypotheses. Additional published analyses of UKCTOCS data suggested a mortality benefit for CA-125 ROCA screening when peritoneal cancer cases were excluded and a statistical test assigning greater weight to later years of the trial was used. In the UKCTOCS trial, a greater proportion of cancers was identified as peritoneal in the CA-125 ROCA group than in the no screening group (5% vs 2%). Excluding cases with high mortality could heighten differences between the CA-125 ROCA and control groups. Excluding peritoneal cancers and relying on protocol-specified statistical testing, there was not a statistical difference in ovarian cancer mortality. Another planned analysis of UKCTOCS aimed to remove certain prevalent ovarian cancer cases selected based on stored CA-125 test results, data imputation, and statistical modeling. Results of that analysis are potentially hypothesis generating but are more subject to bias than the full intention-to-treat analysis of the trial.

Additional analyses of PLCO trial data include a recently published analysis adding up to 6 years of posttrial mortality data (mean, 2.3 years) to the PLCO trial and did not find evidence of a longer-term benefit of screening.[35]

The high mortality and low 5-year survival among all women diagnosed with ovarian cancer may be attributable to continued challenges detecting the disease at an early stage.[44] In PLCO, there was no statistically significant difference in the proportion of cases identified at the localized stage in the intervention vs usual care group (15% vs 10%, respectively; $P = .08$). Comparisons by stage and group also were not statistically different when comparing localized and regional cancer cases with more advanced cancers. In the UKCTOCS trial, a greater proportion of cases was identified at the localized stage (stage I) with CA-125 ROCA screening (36%) and transvaginal ultrasound screening (31%) compared with the control group (23%) ($P < .005$). The overall differences by group and stage were also statistically significant when comparing localized and regional cancers (stages I and II) with more advanced cancers (stages III and IV).[31] Although no overall mortality benefit was associated with these observed stage shifts, these comparisons are relevant because of clinical differences in treatment strategies between stage I and higher-stage ovarian cancer (ie, need for adjuvant radiation therapy); treatment outcomes in the UKCTOCS trial have not yet been published.

Cancer type is also important, as it defines 2 broad categories of epithelial ovarian cancer with shared clinical and histological features that represent distinct models of epithelial ovarian carcinogenesis.[45] Type I tumors include low-grade, generally indolent tumors, which are often associated with somatic mutations in a number of genes (eg, *KRAS*, *BRAF*, *ERBB2*) and develop from benign extraovarian lesions implanted on the ovary.[16,17,46] Type II tumors are more likely to derive from the fallopian tube or ovarian surface epithelium. These cancers are generally high grade and are genetically unstable, including high rates of *TP53* and *BRCA* mutations.[16,45] The UKCTOCS trial reported cancer types diagnosed

Table 5. Summary of Evidence

Test	No. of Studies (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations (Includes Reporting Bias)	Overall Study Quality	Applicability
KQ1: Benefits of Screening						
Annual screening with CA-125 testing	2 RCTs (n = 173 858)	Screening with CA-125 did not result in improved ovarian cancer mortality compared with no screening (UKCTOCS[31]: HR, 0.89 [95% CI, 0.74-1.08]; UK Pilot[33]: RR, 0.50 [95% CI, 0.22 -1.11])	Consistency: Reasonably consistent Precision: Reasonably precise	Follow-up not available beyond 10 y for a substantial proportion of UKCTOCS trial participants Reporting bias undetected	Good	Trial evidence from the United Kingdom where screening occurred in specialized trial settings and cancer treatment was provided through the National Health Service, which is a more centralized health system relative to the United States Study enrolled mostly white women UKCTOCS[31] began in 2001 FDA does not support ROCA screening algorithm
Annual TVU examination	1 RCT (n = 151 922)	TVU screening did not result in improved ovarian cancer mortality compared with usual care (UKCTOCS[31]: HR, 0.91 [95% CI, 0.76-1.09])	Consistency: NA Precision: Reasonably precise	Follow-up data incomplete beyond 10 y for a substantial proportion of trial participants Reporting bias undetected	Good	Trial evidence from the UK where screening occurred in specialized trial settings and cancer treatment provided through the National Health Service, which is a more centralized health system relative to the United States Study enrolled few nonwhite participants
Annual CA-125 testing + TVU examination	1 RCT (n = 68 557)	No reduction was found in ovarian cancer mortality from combined TVU and CA-125 screening compared with usual care (PLCO[21]: RR, 1.18 [95% CI, 0.82-1.71])	Consistency: NA Precision: Reasonably precise	Changes to protocol, ovarian palpation dropped after first 4 trial years Reporting bias undetected	Good	US multisite trial with usual care control condition and referral to community clinicians for women screening positive Majority white, non-Hispanic study participants Trial begun in 1993
KQ2: Harms of Screening						
Annual screening with CA-125 testing	3 RCTs (n = 242 415)	The false-positive rate over multiple rounds of screening in the largest trial was 44%. Complications from CA-125 testing were generally minor and ranged from 0.86 per 10 000 screens to 58.3 per 10 000 women. False-positive surgery occurred in 0.2% to 1% of those screened with CA-125. One larger trial (n = 151 923) reported complications in 3.1% of false-positive operations. One smaller trial (n = 21 935) reported no surgical complications. Psychological harms were reported in a subset of 1 trial. No statistically significant differences were found in psychological outcomes between the screening and no screening groups; increased psychological morbidity risk among women recalled for higher-level screening.	Consistency: Reasonably consistent or NA Precision: Reasonably precise	Psychological harms measured only for subsets of trial participants Reporting bias undetected	Good	Trial evidence from the United Kingdom, where screening occurred in specialized trial settings and cancer treatment provided through the National Health Service, which is a more centralized health system relative to the United States
Annual TVU examination	2 RCTs (n = 220 479)	A false-positive rate of 12% was reported in the initial screening round Complications from screening with TVU ranged from 1.86 per 10 000 screens to 3.3 per 10 000 women False-positive surgery occurred in 3.2% of those screened with TVU Complications occurred in 3.5% of false-positive operations. Psychological harms were reported in a subset of 1 trial No statistically significant differences were found in psychological outcomes between the screening and no screening groups	Consistency: Reasonably consistent or NA Precision: Reasonably precise	Psychological harms measured only for subsets of trial participants Data on cumulative false-positive rate not reported Reporting bias undetected	Good	Screening conducted in specialized trial centers Treatment for cancer (in all study groups) was through the centralized National Health Service system in the United Kingdom and in community care settings in the United States

(continued)

Table 5. Summary of Evidence (continued)

Test	No. of Studies (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations (Includes Reporting Bias)	Overall Study Quality	Applicability
Annual CA-125 testing + TVU examination	2 RCTs (n = 68 849)	A false-positive screening rate of 10% over the course of the screening program. False-positive surgery occurred in 3% of women that did not have ovarian cancer; complications occurred in 15% of these operations. Women with abnormal test results (n = 32) compared with women with no abnormal results more likely to report cancer worry at 2-y follow-up (OR, 2.8 [95% CI, 1.1-7.2])	Consistency: Consistency NA Precision: Reasonably precise (except psychological harms imprecise)	Psychological harms measured only for subsets of trial participants Reporting bias undetected	Fair to Good	US-based, multisite trial Pragmatic trial with usual-care control condition and referral to community clinicians for women screening positive Majority white, non-Hispanic participants

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; NA, not applicable; OR, odds ratio; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; QUEST, Quality of life, Education, and Screening Trial; RCT, randomized clinical trial; ROCA, risk of ovarian cancer algorithm; RR, risk ratio; TVU, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

by study group, with a higher percentage of cases identified as type II in the control condition and more borderline and nonepithelial types observed in the screening groups.[31] An analysis of data from the PLCO trial found that type II tumors were less likely diagnosed from screening and were diagnosed at a later stage. The authors suggested that overdiagnosis of more indolent cancer types could, in part, account for the lack of a mortality benefit from ovarian cancer screening in the trial.[11] Recent work to refine the distinctions among ovarian cancer molecular, pathological, and clinical characteristics highlights a growing understanding that survival differences are more likely attributable to cancer type than stage at diagnosis, with the most common type II cancers being particularly lethal regardless of stage, owing to microscopic metastases.[15,16] Even stage I cancers in some type II high-grade epithelial carcinomas may have microscopic metastases, because cancer cells can be present in ascites (stage Ic).[14,16,47,48]

Although no significant difference in mortality was found in the more recent UKCTOCS trial, advances were made in reducing the number of women without cancer who underwent diagnostic surgery, compared with earlier trials. The UKCTOCS trial took a more nuanced and regimented approach to CA-125 testing and triage by using an algorithm that incorporates CA-125–level trajectories to assign 3 levels of risk, with protocol-driven surveillance and triage testing for follow-up. Accordingly, surgery rates were lower in the CA-125 ROCA group than in the transvaginal ultrasound–only group of the trial and also compared with screening in the PLCO trial (1% vs 3%).

In addition, surgical complication rates were lower in the UKCTOCS trial than in the PLCO trial. Fifteen percent of women without cancer who underwent surgery experienced a major complication in the PLCO trial, compared with just more than 3% in the UKCTOCS trial. Differences in study setting could partly account for this, because diagnostic testing in the PLCO trial was conducted through referrals to women's routine sources of care and not necessarily specialized tertiary care settings. In contrast, in the United Kingdom, all women referred for diagnostic testing were seen at National Health Service tertiary care surgical centers. Regardless of the complication rates, however, high rates of surgery and removal of a single ovary or both ovaries in the absence of disease occurred in both trials.

Evidence from a recent systematic review reported on health effects associated with bilateral salpingo-oophorectomy at the time of benign hysterectomy.[49] Removal of the ovaries, in the absence medical indication, may affect cardiovascular health, all-cause mortality, mental health, and sexual function. In addition to potential surgical complications that could accompany the removal of women's ovaries, fallopian tubes, or both at the time of a surgical investigation for a false-positive screening test, harms from ovary removal without indication cannot be ruled out.[49-51] At the same time, there is evidence that having an oophorectomy, salpingectomy, or tubal ligation may reduce risk of ovarian cancer.[49,51] Further research is needed to assess net effects on women's future health of the removal of ovaries and fallopian tubes in the context of screening trials and other medical procedures.

No ongoing randomized trials of ovarian cancer screening using new screening tools were identified. While some tools in development may hold promise for the future (eg, microRNA),[47] currently there are no new screening tools (ie, biomarkers, instruments) exhibiting levels of test performance beyond what is observed for the screening tools evaluated in trials. Efforts to improve on the ROCA algorithm by adding more protein markers along with CA-125 are under way using data from the UKCTOCS trial. Given the absence of a single marker or screening device that is effective for ovarian cancer, research is likely to increasingly aim to identify new markers and combinations of markers for use in prediction models.[52]

Limitations

This review has limitations related to the types of evidence considered. Observational evidence was not included, owing to the availability of adequately powered trials that can estimate the mortality reduction from screening relative to an unscreened group. These trial comparisons summarize the net effect of screening, detection, and treatment[6] and are considered by the USPSTF to be the highest level of evidence for screening recommendations.[6] Given the low incidence of ovarian cancer, very large trials are necessary to determine whether benefits of a screening program outweigh harms, which for ovarian cancer include surgery and ovarian removal.

The strict inclusion and exclusion criteria related to study design and outcome reporting excluded evidence from 2 large studies: the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS)

trial[53] and the University of Kentucky Ovarian Cancer Screening Trial.[54] Inclusion of these studies would not have changed the review conclusions.

Randomized trial evidence can have limitations in terms of generalizability and applicability to usual care. Nearly all trial participants in the UKCTOCS trial were white women, and just 12% of women enrolled in the PLCO trial identified as of minority race or ethnicity. The PLCO trial is potentially more applicable to a US setting than the UKCTOCS trial, given differences in health care systems and the referral to usual care for treatment in the PLCO trial. The low surgical complication rates from surgery seen in the UKCTOCS trial, for example, may have been attributable to the receipt of care in tertiary care centers. It is also possible that screening tests offered through a trial might would be more accurate than screening in routine care or that surgical investigations might be more common in the absence of trial protocols. In addition, the definition of false-positive surgery may underestimate surgical harms, given the absence of a mortality benefit from ovarian cancer screening. Surgery undertaken on the basis of screening, even when cancer was diagnosed, did not lead to significantly reduced mortality from ovarian cancer.

Conclusions

In randomized trials conducted among average-risk, asymptomatic women, ovarian cancer mortality did not differ between screened women and those with no screening or in usual care. Screening harms included surgery (with major surgical complications) in women found to not have cancer. Further research is needed to identify effective approaches for reducing ovarian cancer incidence and mortality.

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Author Contributions: Dr Henderson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Henderson, Webber.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Webber.
Supervision: Henderson, Sawaya.

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