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Screening for Ovarian Cancer: An Updated Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Importance: Ovarian cancer, while not common, is the fifth-leading cause of cancer death among United States women. In 2012 the U.S. Preventive Services Task Force (USPSTF) determined that harms of ovarian cancer screening outweighed benefits based on trial evidence, and recommended against screening average-risk women.

Objective: To update the previous systematic review and inform USPSTF ovarian cancer screening guidance.

Data Sources: MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials from January 1, 2003, through January 31, 2017, and prior literature identified in the previous review conducted for the USPSTF.

Study Selection: English-language trials of benefits and harms of screening for ovarian cancer in average-risk women reporting health outcomes (e.g., mortality and quality of life). Interventions compared with the control condition were transvaginal ultrasound screening alone, ultrasound screening with cancer antigen 125 (CA-125) testing, and CA-125 screening alone—either with a single measurement threshold value or measures of change over time.

Data Extraction and Synthesis: Two investigators independently reviewed abstracts and full-text articles, and then extracted data from fair- and good-quality trials.

Main Outcomes and Measures: Ovarian cancer mortality and incidence (defined as ovarian, fallopian tube, and peritoneal cancer), ovarian cancer survival, harms associated with false positive test results, false positive surgery, screening and surgical complications.

Results: Four RCTs (n = 293,587) were included; three reported ovarian cancer mortality (KQ1) and all reported potential harms of screening (KQ2). Three trials were rated good-quality and the small trial (n= 549) reporting only on psychological harms of screening was rated fair-quality. Two trials were conducted in the United States and two in the United Kingdom, primarily with postmenopausal, average-risk women. The Prostate, Lung, Colorectal and Ovarian (PLCO) (n = 68,557) included 4-6 rounds of annual CA-125 (≥35 U/mL threshold) and transvaginal ultrasound screening, with up to 13 years of trial data. The U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) (n = 202,546) included 7–11 rounds of either annual transvaginal ultrasound screening or CA-125 screening using the Risk of Ovarian Cancer Algorithm with up to 14 years of trial data. A smaller U.K. Pilot trial (n = 21,935) included three rounds of annual screening with CA-125 (≥30 U/mL threshold) and up to 8 years of trial data. In all three screening trials, there was not a statistically significant difference in ovarian cancer mortality associated with screening. Mortality estimates from the PLCO (RR =1.18 [95% CI, 0.82 to 1.71]) or in either arm of the UKCTOCS: ultrasound (HR = 0.91 [95% CI, 0.76 to 1.09]) and CA-125 (HR = 0.89 [95% CI, 0.74 to 1.08]) were based on more rounds of screening and larger study populations. Harms of screening in these two large screening trials included surgical investigations among screen-positive women without cancer, which ranged from 1 percent of trial participants without cancer screened with CA-125 testing in the UKCTOCS, and 3.2 percent for the ultrasound arm of the UKCTOCS and in the PLCO screening intervention. Serious

surgical complications of occurred for just over 3 percent of women without cancer in the UKCTOCS intervention arms, and in 15 percent of women in the PLCO intervention arm. Evidence on psychological harms was limited but nonsignificant, except in the case of repeat followup scans and tests, which increased the risk of psychological morbidity in a subsample of the UKCTOCS participants based on the General Health Questionnaire 12 (score ≥4) (OR 1.28 [95% CI, 1.18 to 1.39]).

Conclusions and Relevance: Since the previous review for the USPSTF, results from a large trial conducted in the United Kingdom were published. Ovarian cancer mortality did not differ between control and intervention screening conditions in any of the included trials, including two good-quality studies with adequate power to detect differences. Harms of screening include surgery following a false positive test, often resulting in removal of one or both ovaries and/or fallopian tubes, and the potential for major surgical complications. Reports from the UKCTOCS of a potential delayed effect of screening on ovarian cancer mortality require further followup data to evaluate, but the causal mechanism for a delayed screening effect is unclear. Major trials of promising ovarian cancer screening tools have null findings to date among healthy average-risk women, and there are considerable harms associated with screening.

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Chapter 1. Introduction

Definition of Ovarian Cancer

Ovarian cancer includes cancers of the ovary, fallopian tubes, and peritoneum due to the origination from similar tissue types and similar clinical management and treatment.[1] Epithelial ovarian cancer is classified into five subtypes, based on histology to identify the origin and degree of differentiation: high-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, low-grade serous carcinoma, and mucinous carcinoma.[2] Most ovarian cancers are included in these subtypes, with the remainder being rare non-carcinoma types include germ cell tumors, sarcomas, sex cord-stromal tumors. Overall, 10-15% of ovarian cancers are considered borderline, having low malignant potential. The staging of ovarian cancer follows National Cancer Institute definitions describing the extent of tissue involvement and spread with the terms in situ, localized, regional, distant (outside the peritoneum), and unknown.[3] Detailed staging categories for ovarian cancer established by the International Federation of Gynecology and Obstetrics (FIGO) describe the specific characteristics used to assign stages I through IV, as well as staging within these levels.[4, 5]

Prevalence and Burden

Ovarian cancer is the ninth most common cancer, and fifth most common cause of cancer death, in U.S. women, with approximately 1.3 percent of women being diagnosed with ovarian cancer at some point in their lives.[6] According to data from the Surveillance, Epidemiology, and End Results Program (SEER) and National Program of Cancer Registries, the average annual age-adjusted incidence of ovarian cancer in the U.S. was 11.6 cases per 100,000 women for 2009-2013 with a mortality rate of 7.5 per 100,000 women. The incidence of ovarian cancer has declined slightly since the mid-1970s with an average of 1.9 percent a year over the last 10 years.[2, 6] The majority of women diagnosed with ovarian cancer are over age 45 (88%), with a median age of diagnosis of 63 years. The average annual incidence of ovarian cancer varies by race and ethnicity, occurring most frequently in white women (12.0 per 100,000) followed by Hispanic women (10.3 per 100,000). Rates are similar for black women (9.3 per 100,000 women) and Asian/Pacific Islander (9.0 per 100,000), and lowest for American Indian/Alaska Native women (8.5 per 100,000), although estimates are less precise for this subpopulation.[6, 7]

Etiology and Natural History

Ovarian cancers can originate from ovarian, fallopian, or other tissue types (e.g., endometrium, peritoneum).[2, 8] Historically, ovarian carcinomas were assumed to derive from the ovarian surface epithelium; however, evidence increasingly indicates that high-grade intraepithelial lesions in the fallopian tubes may become malignant and spread to the ovarian epithelium and peritoneum.[9] Two broad categories defined by shared clinical features have been developed to better represent distinct models of epithelial ovarian carcinogenesis.[10] Type I tumors include low-grade, generally indolent tumors, that are often associated with somatic mutations in a

number of genes (e.g., *KRAS*, *BRAF*, *ERBB2*) and develop from benign extra-ovarian lesions implanted on the ovary.[9, 11, 12] 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.[9, 10]

Overall, mortality from ovarian cancer is high, with fewer than half (46%) of women surviving for at least 5 years following an ovarian cancer diagnosis.[6] By comparison, overall 5-year survival rates for cancers of the breast (90%), endometrium (80%), and cervix (70%) are much higher. The high mortality and low 5-year survival among all women diagnosed with ovarian cancer is largely due to challenges detecting the disease at an early stage. Only 15 percent of cases are diagnosed at the local stage, when 5-year survival is favorable at 92 percent. Over 60 percent of cases are diagnosed after the cancer has distant metastases. With distant spread, the 5 year survival drops to 29 percent.[6] The aggressive nature and advanced stage at diagnosis lead to a poorer prognosis for type II ovarian cancers, with 30 percent of patients surviving at 5 years, compared to 55 percent of patients with type I cancers.[10] Non-Hispanic black women have the lowest 5-year survival rates, and the second-highest mortality rates (7 per 100,000), slightly lower than the mortality rates observed among non-Hispanic white women (8 per 100,000).[13] Ovarian cancer mortality increases with age at diagnosis with the highest rates of death among women 65 to 74 and a median age of death of 70 years.[6]

Risk Factors

Multiple modifiable and nonmodifiable factors have been associated with an increased risk for developing ovarian cancer including: increasing age, family history of ovarian cancer, inherited genetic mutations (e.g., *BRCA1*/*BRCA2*), obesity, nulliparity, use of hormone replacement therapy, and increased numbers of lifetime ovulatory cycles.[2, 14] Most risk factors show significant heterogeneity across ovarian cancer subtypes.[15] Approximately 20 percent of ovarian cancers are familial, with the presence of cancer in multiple first- or second-degree relatives being an indicator of inherited cancer syndrome.[1] Inherited mutations are associated with 5 to 15 percent of all ovarian carcinomas. The most common high-risk genetic syndromes include hereditary breast and ovarian cancer ((i.e., *BRCA1* and *BRCA2*), Lynch, Li-Fraumeni, and Peutz-Jeghers Syndromes.[2, 16-20] In addition, genome-wide association studies have identified as many as 17 common low-penetrance alleles associated with ovarian cancer.[2, 21-26] Women with a greatly increased risk for developing ovarian cancer, defined by the presence of germline genetic mutations, may benefit from risk-reducing surgery or chemoprevention. For these women genetic counseling is recommended, including a discussion of the risks and benefits of prevention.[27-29]

Several factors have been identified that are associated with a decreased risk of ovarian cancer. Among the most well established is the use of oral contraceptives, with one large study finding a 20 percent decrease in the risk of ovarian cancer for every 5 years of use.[2, 30] This protective effect may be due to the suppression of ovulation and the associated hormonal and inflammatory process which may be associated with the etiology of ovarian carcinomas.[2, 30] Parity also has a protective effect, with estimates of a 30 to 40 percent decrease in the risk of cancer associated with a first pregnancy, and 10 to 15 percent decrease in each subsequent pregnancy.[2, 31]

Breastfeeding is also associated with decreased risk.[2, 32-35] However, these identified lifestyle and hormonal risk factors as mainly associated with a decreased risk of the less lethal Type I ovarian cancers with more modest effects on the prevention of Type II cancers (e.g., high-grade serous-carcinoma).[2, 36]

Risk-prediction models have been developed to identify women at increased risk of developing ovarian cancer based on personal and family history. To date, for women at average genetic risk, these tools have not been found to have a strong predictive performance, likely due to the relative rarity of ovarian cancer and the modest effect size of known risk factors.[2, 37-40]

Prevention

While the use of risk-reducing surgery has generally been advocated for women at high genetic risk,[2, 41] there is some evidence[42, 43] from observational studies that it may also be associated with a decreased risk of for women at average or unknown genetic risk. Bilateral salpingo-oophorectomy (BSO) is associated with reduced risk of ovarian cancer in women at average and high risk of disease; however, the risk reduction is not 100 percent, and has been associated with potential risks and side effects including: early menopause, osteoporosis, cardiovascular disease, and increased overall mortality.[2, 44] Bilateral salpingectomy, even with ovarian retention, may be effective in preventing ovarian cancer as there are subtypes postulated to arise in the fallopian tubes. Salpingectomy may allow high-risk women to delay removal of the ovaries, and when performed during a planned hysterectomy, may reduce risk for average-risk women.[2, 45, 46] Based on evidence of the distal fallopian tube epithelium as the site of origin for at least some cancers the Society for Gynecologic Oncology (SGO) and the American Congress of Obstetricians and Gynecologists (ACOG) have issued statements recommending consideration of opportunistic bilateral salpingectomy to reduce ovarian cancer mortality in the general population.[2, 47, 48] Tubal ligation and hysterectomy have also been associated with reduced risk of ovarian cancer; however, no groups have recommended these procedures as prevention strategies.[2, 49]

In addition to surgical intervention, hormone-modulating prescription drugs such as oral contraceptives have been investigated for prevention of ovarian cancer.[2, 30] The SGO has stated that appropriate counseling about side effects and contraindications for oral contraceptive use can allow patients to weigh the risks and benefits of their use for cancer prevention.[50] Of note, a 2013 systematic review for the AHRQ Effective Healthcare Program did not find sufficient evidence to recommend oral contraceptive use only for the purpose of primary prevention of ovarian cancer.[51]

Diagnosis and Treatment

Definitive diagnosis and staging of ovarian cancer requires surgery.[1, 2, 28] Most women with newly diagnosed ovarian cancer undergo primary debulking surgery to remove as much of the visible tumor as possible. This surgery may include hysterectomy, BSO, and omentectomy.[1, 28] Younger patients with early (stage I or II) and/or low-risk tumors who wish to preserve fertility may opt for unilateral salpingo-oophorectomy.[1] Survival is improved for women with complete

tumor resection. In cases where total resection is not possible or contraindicated, neoadjuvant chemotherapy can reduce tumor size and facilitate later resection. Most women respond well to initial treatment; however, the majority will experience recurrence of the disease, requiring a cycle of repeated surgeries and chemotherapy cycles.[1, 2] Treatment within high-volume hospitals and by gynecologic oncologists has been associated with guideline-adherent treatment and improved survival in ovarian cancer [2, 52-54]

Rationale for Screening

The symptoms of ovarian cancer are often nonspecific, including bloating, pelvic or abdominal pain, urinary symptoms, vaginal discharge, increased vaginal bleeding, or gastrointestinal problems.[1, 2] These symptoms are often not seen as symptoms of serious illness by women or providers.[2] As many as 95 percent of all women in primary care report one of the symptoms of ovarian cancer in the previous year, with 72 percent of women having recurring symptoms, most commonly back pain, fatigue, indigestion, urinary tract problems, constipation, and abdominal pain.[55] While women found to have ovarian cancer appear to have symptoms more frequently and with a higher severity, the frequency of reported symptoms in unaffected women poses a challenge for clinical detection.[55] Efforts to generate clinical decision tools based on the presence of combinations of symptoms, such as the Ovarian Cancer Screening Index,[56] have been found to have a higher sensitivity than individual symptoms; however, estimates for the accuracy of these tools indicate that they are not sufficiently specific for implementation in clinical practice.[57] Because of the lack of specific symptoms, research has investigated the use of other strategies for early detection, including the use of biomarkers and imaging technologies.

Screening Strategies

The most widely tested screening approaches, with reasonable test performance characteristics, have broadly focused on identifying abnormalities in the physical structure of the ovary or detecting increased CA-125 levels or trends. The most complex screening strategies involve algorithms that use CA-125 levels measured over time to compute the likelihood of ovarian cancer and determine surveillance and surgical investigation protocols at different risk thresholds.[2, 58-61] Transvaginal ultrasound (TVU) is the most widely used imaging technique for gynecologic symptoms and pathologies, but the majority of adnexal masses identified by TVU are benign.[2, 62]

Elevated CA-125 levels have been noted in women with an advanced ovarian carcinoma at diagnosis, leading to its proposed use as a potential biomarker for early detection.[2] Some limitations with regard to the assay's specificity and sensitivity have been recognized, as CA-125 may be markedly elevated in patients with a variety of benign or non-ovarian malignant conditions. In addition, serum CA-125 has been found to be significantly elevated in only half of women diagnosed with stage I or II ovarian cancer.[2, 63] Efforts to improve the performance of screening with CA-125 led to development of the Risk of Ovarian Cancer Algorithm (ROCA [TM] [Abcodia]). The algorithm uses sequential CA-125 measures taken at annual screening visits to evaluate the trajectory of CA-125 serum over time following a baseline age-adjusted CA-125

measurement.[64]

Another screening strategy that continues to be practiced[65] but is not supported by clinical evidence is ovarian palpation with bimanual pelvic examination. The accuracy of this screening examination (sensitivity 5.1%)[66] does not support its use over more sensitive tools.[67, 68] The practice has been discouraged or recognized as lacking evidence to recommend[68] as a routine screening examination for ovarian cancer due to its high false positive rate and low positive predictive value[69, 70] and potential physical and psychological harms in the absence of benefits.

Research continues into the discovery of other biomarkers and the use of alternative imaging strategies for the early identification of ovarian cancer; however, no other markers have been implemented and tested in an ovarian cancer screening trial.[2]

Current Clinical Practice in the United States

No organizations currently recommend screening for ovarian cancer in the general population. Several groups have issued recommendations against screening in asymptomatic, average-risk women, including the American Academy of Family Physicians,[71] American Cancer Society,[72] American College of Radiology,[73] and American Congress of Obstetricians and Gynecologists.[69] Nonetheless, a 2012 nationally representative sample of over 1,000 family physicians, general internists, and obstetrician/gynecologists found that over one-third of physicians believed that ovarian cancer screening was effective and up to one-fourth routinely offered TVU and/or CA-125 screening to asymptomatic women.[74] Additionally, a 2014 survey of 1,555 U.S. family physicians, general internists, and obstetrician-gynecologists found that 27 percent of physicians overestimated the ovarian cancer risk among women at the same risk as the general population and 65 percent underestimated ovarian cancer risk among women at much higher risk than the general population.[75]

In 2016 the United States Food and Drug Administration (FDA) released a recommendation against using tests marketed for ovarian cancer screening. The FDA stated that there are no ovarian cancer screening tests approved by the FDA and no published clinical information to demonstrate that currently available tests are accurate and reliable in asymptomatic women. In particular the FDA stated that the ROCA algorithm has been marketed in the United States with no data to support its claims for ovarian cancer detection and improved cancer survival.[76] Following this statement from the FDA the company marketing the ROCA test suspended its commercial availability in the United States.[77]

Previous USPSTF Recommendation

In 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against screening for ovarian cancer in women (D recommendation).[70] This recommendation applies to asymptomatic women without a known genetic mutation that increases their risk for ovarian cancer (e.g., *BRCA* mutations). There was adequate evidence that annual screening with TVU and testing for CA-125 in women does not reduce ovarian cancer mortality. In addition, the disease occurs

infrequently enough that most women with a positive screening test results will have a false positive result; therefore, screening for ovarian cancer can lead to important harms, including major surgical interventions and complications in women who do not have cancer. The USPSTF concluded that there was at least moderate certainty that the harms of screening for ovarian cancer outweighed the benefits.

Chapter 2. Methods

Scope and Purpose

This systematic review addresses the benefits and harms of screening for ovarian cancer in women at average risk for ovarian cancer. The USPSTF will use this review to update its 2012 recommendation on this topic.[70]

Key Questions and Analytic Framework

We developed an Analytic Framework (**Figure 1**) and two Key Questions (KQs) to guide the literature search, data abstraction, and data synthesis.

1. Does screening for ovarian cancer in asymptomatic women using a single test or combined algorithm (such as, but not limited to, testing for serum cancer antigen [CA–125] and ultrasonography) 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?

Data Sources and Searches

In addition to considering all studies from the previous reviews on this topic[78-80] for inclusion in the current review, we performed a comprehensive search of MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Collaboration Registry of Controlled Trials. We searched between January 1, 2003 and January 31, 2017, building upon the most recent full search for this topic.[80]

We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian (**Appendix A**). All searches were limited to articles published in English. We managed literature search results using version X7 of Endnote® (Thomson Reuters, New York, NY), a bibliographic management software database.

To ensure comprehensiveness, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were published before our search dates or were not identified in our literature searches.[81, 82]

Study Selection

Two reviewers independently reviewed the title and abstracts of all identified articles using Abstrackr[83] to determine if the study met our *a priori* inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A**). Two reviewers then independently evaluated the full-text article(s) of all potentially relevant studies against the complete inclusion

and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion.

For both KQs we considered randomized controlled trials asymptomatic average risk women, including women of unknown risk, aged 45 and older. Studies focused on screening explicitly among high-risk populations (e.g., *BRCA* mutation carriers, individuals with first-degree relatives with ovarian cancer) were excluded from this review. We included any screening intervention conducted in primary care settings (including obstetrics and gynecology practices) compared with usual care or no screening. When available, as is the case for ovarian cancer screening, RCT evidence is prioritized, particularly when adequately powered to evaluate screening for a rare cancer. Trials that addressed only the accuracy of screening and cancer detection rates without reporting morbidity, mortality, or quality of life data were not included in this review.

For KQ 1 we considered a range of outcomes including: ovarian cancer-specific mortality (including primary peritoneal and fallopian tube cancer), cancer-related morbidity, and quality of life. KQ 2 included the following harms outcomes: mortality from other causes, rates of surgery, rates of false positive screening results, complications of diagnostic surgical procedures, and health and psychological effects of screening tests. Evidence of potential harms associated with screening was limited to trials reporting health outcomes. Effects of screening on quality of life are evaluated as a potential benefit or harm, but this outcome was reported only for harms. Importantly, direct trial evidence on the health outcomes associated with different screening programs (including not screening) offers the summary or net effect of harms and benefits of screening. Disease specific mortality is the key outcome for ovarian cancer rather than all-cause mortality because of the rarity of ovarian cancer, and because the mortality rates from ovarian cancer are quite high. Due to its rarity, ovarian cancer screening intervention effect sizes would not be expected to be large enough to have discernable effects on all-cause mortality. Nevertheless, it is important to compare mortality across study arms to determine whether there are any unexpected increases in other causes of mortality from the screening program, to assess for problems with coding or discernment of cause of death in the trial procedures, and to evaluate whether differential study continuation resulted in unrecognized study arm imbalances in participant risk of death.

Quality Assessment and Data Abstraction

Two reviewers independently assessed the methodological quality of each study using predefined criteria developed by the USPSTF[84]. Disagreements in quality were resolved by discussion. Each study was given a final quality rating of good, fair, or poor.

Good-quality RCTs had adequate randomization procedures and allocation concealment, blinded outcome assessment, reliable outcome measures, similar baseline characteristics between groups, low attrition (≥90% of participants had followup data with <10 percentage point difference in loss to followup between groups), used intention-to-screen analysis, and reported diagnostic criteria for outcome ascertainment. We rated trials as fair quality if they were unable to meet the majority of the good-quality criteria. We rated trials as poor quality if attrition was greater than

40 percent or differed between groups by 20 percentage points, or if there were any other "fatal" flaws that seriously affected internal validity, as agreed upon by two independent investigators.

We abstracted data from all included studies into standard evidence tables using Microsoft Word® (Microsoft Corporation, Redmond, WA). A second reviewer checked the data for accuracy. We abstracted information on study design, baseline data, intervention details, health outcomes, and adverse events.

Data Synthesis and Analysis

Given the small number of studies and heterogeneity of screening interventions, meta-analyses were not conducted for any of the KQs in this report. We instead conducted a narrative synthesis of the results by screening strategy. We generated summary tables and descriptive text detailing the populations and protocols of included studies, and the interventions and followup up procedures of the included trials. The pre-specified outcomes sought for this review were abstracted from each study, by key question, and results were presented in groups defined by the screening strategy.

In 2014, the World Health Organization revised the classification of tumors of the female reproductive system. Following these revisions, most cancers historically classified as peritoneal cancer would be reclassified as ovarian and tubal cancers. Therefore, we present the effect of screening on the combined classifications of ovarian, tubal, and peritoneal cancers.[85] Ovarian cancer was defined as primary ovarian, peritoneal, and fallopian tube cancers in the Prostate, Lung, Colorectal and Ovarian (PLCO). The U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) also reported results for this outcome, but excluded primary peritoneal cancer from the primary analysis. We have noted where we have calculated results that included peritoneal cancer using raw numbers reported in the UKCTOCS. Data from the U.K. Pilot trial did not capture information related to peritoneal cancer; therefore, these results are limited to primary cancer of the ovary and fallopian tubes.

The number of participants stated throughout the report refers to the number analyzed, unless otherwise stated. The tables report both the n randomized and the n analyzed.

Data on false positive rates were calculated as the percent of those without ovarian cancer who received a positive test result. The PLCO[86] defined a positive screen based on the results of the initial screening tests (i.e., positive on TVU or CA-125 screening test). In the UKCTOCS[87] a positive screen was defined as a positive initial screen that eventually led to surgery. The definition used in the PLCO, where the screening test result defines test positives, is consistent with the USPSTF interest in evaluating how the initial test sets in motion a cascade of effects.[88] Each definition, however, provides slightly different insights, so we calculated and report false positive rates based on both definitions.

In accordance with the CONSORT scientific standards for the design and analysis of randomized controlled trials, when multiple statistical tests are reported for key trial outcomes, we prioritize statistical analyses defined *a priori* in the trial protocol.[89]

When reporting study results from the two large trials included in this review, we aimed to provide comparable statistics, and have noted where this required additional calculations.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center approach[90] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[91] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan was posted for public comment on the USPSTF Web site from March 26, 2015, to April 22, 2015. The USPSTF received several comments about the population under consideration, particularly an interest in including women with specific genetic risk factors. Considerations for these populations are generally outside the scope of a review of a broad screening program among asymptomatic women at average risk for ovarian cancer; therefore, the

included population for this topic was not changed. Several comments sought clarification on the analytic framework. In response, the USPSTF simplified the analytic framework to focus on direct evidence from screening trials. A few comments requested that specific screening interventions be evaluated. The USPSTF clarified the inclusion criteria to indicate that all screening tests and approaches evaluated in clinical trials will be included, and added a contextual question to consider whether there are promising screening approaches not yet evaluated by clinical trials. A final research plan was posted on the USPSTF's Web site on March 3, 2015. Additionally, this full draft report was shared with invited expert reviewers and federal partners. We compiled and addressed (where appropriate) the comments received from these invited experts.

USPSTF Involvement

We worked with USPSTF members at key points throughout this review, particularly when determining the scope and methods for this review and developing the Analytic Framework and KQs. After revisions reflecting the public comment period, the USPSTF members approved the final analytic framework, KQs, and inclusion and exclusion criteria. AHRQ funded this review under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

Description of Included Studies

Our literature search yielded 1,381 unique citations. From these, we reviewed the full text of 74 articles. After full text review and critical appraisal, we included 4 trials (published in 17 articles) (**Appendix A Figure 1**). **Appendix B** contains a full list of included studies.

Of the 74 articles that were reviewed, the most common reason for exclusion were not having an included study design (i.e., not RCT) or not reporting a relevant outcome. No trials were excluded based on study quality. **Appendix C** contains a list of all excluded trials and their reasons for exclusion.

Four RCTs (n = 293,587) were included; three reported health outcomes (KQ1), and all reported potential harms of screening (KQ2) (**Table 1**). Two were conducted in the United States[86, 92] and two in the United Kingdom.[87, 93] Analyzed sample sizes ranged from 549 to 202,546 participants. The three trials[86, 87, 93] reporting health outcomes and potential harms were rated good-quality and the small trial[92] reporting only on psychological harms of screening was rated fair-quality.

The following results from the PLCO[86] and UKCTOCS[87] include cases of ovarian, fallopian, and primary peritoneal cancer cases. Data from the U.K. Pilot trial did not capture information related to peritoneal cancer[93]; therefore, these results are limited to primary cancer of the ovary and fallopian tubes.

Included Populations

The two U.K. trials (U.K. Pilot and UKCTOCS) were limited to postmenopausal women aged ≥45 and 50 to 74,[87, 93] the PLCO to women aged 55 to 74,[86] and the Quality of life, Education, and Screening Trial (QUEST) to women aged 30 or older[92] (**Table 1**). Women with a history of bilateral oophorectomy or ovarian malignancy, at increased familial risk of cancer, or with an active malignancy where excluded from the largest U.K. trial.[87] Exclusions were similar for the other trials included for KQ1,[86, 93] but the PLCO additionally excluded women with a history of colorectal or lung cancer, or who had undergone an investigation or treatment for these cancers.[86] The QUEST study, included only for KQ2, also excluded women with plans to become pregnant.[92]

Results of Included Studies

Key Question 1. Does Screening for Ovarian Cancer in Asymptomatic Women Using Single Tests or Combined Algorithms Reduce All-Cause or Disease-Specific Morbidity And Mortality?

Summary

Three trials reporting mortality outcomes had null findings based on *a priori* per protocol statistical analyses testing four screening programs for ovarian cancer. The screening tests evaluated were annual transvaginal ultrasound, annual transvaginal ultrasound and CA-125 serum testing, annual CA-125 testing, and annual CA-125 serum testing interpreted with an algorithm (ROCA) that incorporates changes over time to inform triage and rescreening intervals.

Description of Included Studies

Three large, good-quality trials reported ovarian cancer incidence and mortality for women randomized to ovarian cancer screening versus no screening or usual care. The largest (n=202,546) and most recent trial is the UKCTOCS,[87] which began enrolling trial participants in 2001 through 13 National Health Service centers in England, Wales, and Northern Ireland. Identification of women was centralized using primary care registers, and eligible women received personalized invitations. A smaller included trial (n=21,935) was conducted in the United Kingdom by the same research group in preparation for UKCTOCS (U.K. Pilot).[93] This trial recruited women who had participated in a previous ovarian cancer screening study.[94] The third included trial is the PLCO[86] cancer screening randomized trial, begun in 1993 at 10 clinical screening centers in the United States (n = 68,557). The 10 screening centers developed individual recruitment methods. Women were primarily recruited via direct mail; however, other methods included community outreach and mass media. The 10 screening centers developed individual recruitment methods. Women were primarily recruited via direct mail; however, other methods included community outreach and mass media.[95]

The demographic characteristics of randomized trial participants are described in **Table 2**. In the UKCTOCS and U.K. Pilot trials, the race/ethnic composition of the study population was over 95 percent white.[87, 93] Eighty-eight percent of women in the PLCO[86] were white, non-Hispanic (6% were black, non-Hispanic, 4% were Asian or Pacific Islander, and very few were Hispanic or Native American). The PLCO[86] and UKCTOCS[87] had similar participant age distributions, with over half of UKCTOCS participants between the ages of 56 and 66 at baseline and 65% in the PLCO between the ages of 55 and 64. The U.K. trials[87, 93] included post-menopausal women as young as 45 or 50, whereas the PLCO[86] did not include any women younger than age 55. Nineteen percent of women in UKCTOCS[87] and 27 percent of PLCO[86] participants had had a prior hysterectomy at baseline (without bilateral oophorectomy). Although women with a known elevated familial ovarian cancer risk were excluded, 1.6 percent of women in UKCTOCS[87] reported maternal history of ovarian cancer, and 6.4 percent a maternal history of breast cancer. 17 percent of women in the PLCO [86] reported any family history of breast or ovarian cancer.

All three trials tested annual screening for ovarian cancer with CA-125 and/or transvaginal ultrasound (**Table 3**). The UKCTOCS[87] had two intervention arms and a no-screening control arm (randomized 1:1:2, respectively). Women assigned to CA-125 algorithm screening received CA-125 serum testing, with triage and followup determined by application of the Risk of Ovarian Cancer Algorithm (ROCA) to test result. Three levels of followup, depending on the ROCA result level were assigned: continue annual screening (low risk), repeat CA-125 in 12 weeks (intermediate risk), or repeat CA-125 testing and transvaginal ultrasound in 6 weeks (elevated risk). Persistent abnormalities were referred for surgical investigation at tertiary care health centers in the U.K. National Health Service system. Women in the ultrasound intervention arm had yearly transvaginal ultrasound testing, with repeat ultrasounds scheduled for unsatisfactory or abnormal results and referral to surgical diagnostic testing and recommended treatment through usual care in the U.K., as in the CA-125 screening arm. Women in the intervention arms of the UKCTOCS underwent a maximum of 11 screening rounds with a median of 11.1 years of follow up.[87] The U.K. Pilot[93] trial compared annual CA-125 screening tests to no screening. Women with CA-125 serum levels of 30 U/mL or greater were considered screening test positive, and further evaluated using ultrasonography. Women in the intervention arm of the U.K. Pilot study underwent a maximum of 3 rounds of screening with up to 8 years of follow up.[93] Women in the screening intervention arm of the PLCO[86] received both CA-125 testing and ultrasonography. The cutoff designating an abnormal result on the CA-125 test was serum level of 35 U/mL or greater. Women with abnormal results on either the CA-125 test or ultrasound were referred for additional evaluation by notifying the woman and her usual community physician.[86, 96] The original trial design for PLCO called for screening for only four annual ovarian cancer screening rounds. A modification of the protocol in 1998 extended screening to 6 annual rounds, with the purpose of increasing the power of the trial. During this 2-round extension, only CA-125 was used for screening.[97] Therefore, women in the intervention arm of PLCO underwent a maximum of 6 rounds of screening (4 with CA-125 and ultrasound, 2 with CA-125 alone) with a median of 12.4 years of follow up. Additionally, in the first 5 years of the PLCO, palpation of the ovaries with a bimanual pelvic examination was also included in the screening protocol. This component of the intervention was dropped, however, as no cancers were identified solely on the basis of this screening component.[66]

Screening Adherence and Contamination

In the UKCTOCS[87], 95 percent of women in the ultrasound arm completed at least one screen, and 99 percent of women in the CA-125 ROCA intervention arm completed at least one screen (**Table 4**). Overall 81 percent of screens were attended in the CA-125 ROCA intervention arm and 78 percent were attended in the ultrasound intervention arm. Adherence varied by round, ranging from 47 to 98 percent in the CA-125 ROCA group and 36 to 95 percent in the ultrasound group.[87] In the U.K. Pilot[93] trial, 86 percent of randomized participants completed at least one screen and 71 percent completed all three screening rounds. Adherence in the PLCO[86] was similar, with 78 to 84 percent of participants attending ultrasound screening and 73 to 85 percent of women attending CA-125 screening depending on the screening round. Rates of screening contamination in the control group were not reported in the U.K. Pilot[93] trial, but were below 5 percent in the UKCTOCS[87] and PLCO[86].

Ovarian Cancer Incidence

The incidence of ovarian cancer did not differ significantly between study arms in any of the included trials. In the UKCTOCS[87] ovarian cancer was diagnosed 0.7 percent of those in the CA-125 ROCA arm (354 cases), and 0.6 percent of those in the ultrasound arm (324 cases) and control arm (645 cases). The incidence rate of ovarian cancer was 6.4 per 10,000 person-years in the CA-125 ROCA screening arm, and 5.9 per 10,000 person-years in both the ultrasound and no screening control arms. In the PLCO,[86] ovarian cancer was diagnosed in 0.6 percent (212 cases) of those in the intervention arm and 0.5 percent (176 cases) of those in the usual care arm (RR 1.21 95% CI, 0.99 to 1.48). In the U.K. Pilot trial, ovarian cancer was diagnosed in 0.1 percent (16 cases) of women in intervention arm and 0.2 percent (20 cases) in the no-screening arm. The low incidence may be due to smaller sample sizes, or the fact that women underwent a prevalence screen 10 years prior to the study. Incidence rates were not reported for the U.K. Pilot trial.[93]

Ovarian Cancer Mortality

CA-125 Screening

The UKCTOCS[87] and U.K. Pilot[93] trial included intervention arms that compared CA-125 screening to no screening (**Table 5**). Although both of the trials used an initial CA-125 screening test to determine followup, the U.K. Pilot study used a single cutpoint to refer participants to further evaluation (CA-125 $\geq$ 30 u/ml), and the UKCTOCS used the ROCA algorithm[98] to triage intermediate and high CA-125 ROCA results for repeat screening and ultrasound. (This ROCA CA-125 screening arm was described as multimodal screening in the UKCSTOCS trial publications.) In the UKCTOCS ovarian cancer mortality in the intervention arm and control arm was similar (IG: 0.32% versus CG: 0.35%) and in survival analysis was 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 based on *a priori* statistical testing with a Cox proportional hazards model (HR = 0.89 [95% CI, 0.74 to 1.08]).[87]

The smaller U.K. Pilot[93] trial (n = 21,935) was designed to assess feasibility and performance of screening and was not powered to test mortality differences. There were 9 ovarian cancer deaths in the intervention group (0.08%) and 18 in the no-screening comparison group (0.16%); the difference was not statistically significant e (RR 0.5 [95% CI, 0.22 to 1.11]). A statistically significant difference in survival between women with index cancers in the IG and the CG was observed when computed from the date of randomization (IG median 72.9 months, CG median 41.8 months; p=.01). This finding was based on a small number of events, and only 6 of 16 index cancers identified in the intervention arm were screen detected. Survival in the control group noted by the study authors as being unusually poor.

Ultrasound Screening

The ultrasound screening intervention arm in the UKCTOCS[87] did not reduce ovarian cancer mortality compared with no screening (**Table 5**). Ovarian cancer mortality in the intervention

arm and control arm was similar (IG 0.32% versus CG 0.35%) and in survival analysis was 3.0 per 10,000 person-years in the intervention group and 3.3 per 10,000 person-years in the comparison group (HR 0.91[95% CI, 0.76 to 1.09]).[87]

Combined CA-125 and Ultrasound Screening

The incidence of ovarian cancer mortality in the PLCO[86] was 3.1 per 10,000 person-years in the intervention arm and 2.6 per 10,000 person-years in the usual care comparison arm. There were 118 deaths in the intervention group (0.34%) and 100 deaths in the control group (0.29%), a not statistically significant difference (RR 1.18 [95% CI, 0.82 to 1.71]). Survival with ovarian cancer did not differ significantly between study arms when estimated from the date of diagnosis (p=0.18) and from the date of randomization (p=0.67), which better accounts for possible lead-time bias (**Table 5**).[86]

Quality of Life

Two studies addressed changes in quality of life associated with ovarian cancer screening, [92, 99] both with regard to potential anxiety associated with ovarian cancers screening. These results are therefore are reported for Key Question 2 as potential harms.

Ovarian Cancer Morbidity

There were no differences in treatments by study arm in the PLCO; 81 percent in the intervention group received surgery plus systemic therapy, compared with 80 percent in the usual care group.[86]

Key Question 2. What Are the Harms of Screening for Ovarian Cancer, Including Harms of the Screening Test and of Diagnostic Evaluation?

Summary

Four trials reported on the harms of ovarian cancer screening. False positive rates and surgical harms were highest among screening programs including transvaginal ultrasound with or without CA-125 measurement. Major surgical complications as estimated in the two largest trials occurred in women with investigations from screening that did not lead to a cancer diagnosis, ranging from 3 to 15 percent of surgeries. The screening tests themselves resulted in minor complications, at rates widely ranging based on study specific definitions from 0.86 to 58.3 per 10,000 screens/women for CA-125 test blood draws (e.g., fainting, bruising) and from 1.86 to 3.3 per 10,000 screens/women for ultrasound testing (e.g., pain, discomfort, infection, bruising).

Description of Included Studies

Evidence on false positive rates and surgical harms of screening were included from the three trials[86, 87, 93] included for KQ1. A substudy of the UKCTOCS[99] (n=23,374) and an additional fair-quality trial (QUEST)[92] (n=549) aimed at evaluating the effects of ovarian cancer screening on quality of life (QoL) and psychological outcomes are described below.

False Positive Rates and Complications

CA-125 Screening

False positive rates calculated for screening with CA-125 across all rounds of the U.K. Pilot trial were 4.2 percent.[93] In the UKCTOCS the false positive rate in the prevalence round of screening was 9.0 percent[64] and cumulatively across all subsequent incidence rounds of the UKCTOCS the false positive rate rose to 44.2 percent with a total of 44.3 percent of women screened receiving a positive test result at least once[64] (**Table 6**). Screening test complications were minor for CA-125 screening, including bruising, fainting, and pain. These complications were reported to occur for 0.86 per 10,000 screens in UKCTOCS[87] and 58.3 per 10,000 women in the PLCO.[86]

False positive surgeries, defined as surgery following a positive screening among women found to have normal or benign adnexa, occurred in nearly 1 percent of those in the CA-125 ROCA arm of the UKCTOCS[87] (n = 488) and 0.2 percent of those screened in the U.K. Pilot (n=23).[93] In the UKCTOCS, one or more major complication occurred in 3.1 percent of false positive surgeries in the CA-125 ROCA arm and included: infection, injury to hollow viscus, anesthetic complications, and cardiovascular and pulmonary events.[87] No surgical complications were reported among the women undergoing surgical investigations in the U.K. Pilot trial.[93]

Ultrasound Screening

False positive rates calculated based on the results of the initial screening using ultrasound occurred in 11.9 percent in the prevalence screening round of the UKCTOCS[64] (**Table 6**). The false positive rate from subsequent rounds was not reported for this arm. Complications from transvaginal ultrasound screening in the UKCTOCS included pain, cystitis or other infection, discomfort, bruising, and fainting, as well as others (unspecified), among 1.86 per 10,000 screens.[87] In the PLCO complications from transvaginal ultrasound occurred in 3.3 per 10,000 women.[86]

False positive surgeries (benign findings on a screen positive investigation) occurred in 3.2 percent of women in the ultrasound arm of the UKCTOCS.[87] Major complications occurred in 3.5 percent of these surgeries and included: injury to hollow viscus, hemorrhage, anesthetic complication/myocardial infarction, hernia, deep vein thrombosis/pulmonary embolism, wound breakdown, bowel obstruction, wound/supravaginal hematoma, infection, and pain with readmission or further operation.[87]

Combined CA-125 and Ultrasound Screening

The combined CA-125 and ultrasound intervention used for the PLCO[86] had a 9.6 percent cumulative false positive rate across all rounds of screening (**Table 6**). Complications from each screening component are discussed above.

False positive surgeries (benign findings on a screen positive investigation) occurred in 3.2 percent of women undergoing combination screening in the PLCO. Major complications occurred in 15.1 percent of surgeries, with benign findings in the PLCO including: infection,

direct surgical harms, cardiovascular/pulmonary events, and other adverse events that were not specified. [86]

Deaths From Other Causes

The UKCTOCS provided data on causes of death other than ovarian cancer, and the PLCO provided data on causes of death other than ovarian, colorectal, and lung cancers. There were no statistically significant differences in causes of death in screening arms compared with control arms.

Psychological Harms of Screening

A study of the psychological morbidity associated with ovarian cancer screening was undertaken within the UKCTOCS (n=23,374).[99] A random sample of women was drawn at baseline from each trial arm (n=1,339) and a survey was administered annually for 7 years to obtain variables for evaluating psychological effects of screening. Similar data were also collected for women in the screening arms who were at any time recalled for followup testing (CA-125 ROCA: n = 12,357; ultrasound: n = 9,678). For the event group, upon abnormal results and recall, questionnaires were administered, and thereafter on an annual basis.[99] The main measures were the Spielberger State/Trait Anxiety Inventory (STAI)[100] and the General Health Questionnaire 12 (GHQ-12)[101] for evaluating psychological morbidity. A small but statistically significant difference in the education levels of women between the MSS and ultrasound group of the random samples was observed, and in the event sample more women reported hormone replacement therapy use than in the random sample (21% versus 14%, $p<.001$).[99] In light of these unexpected imbalances, the study authors recommended cautious interpretation of findings. In adjusted analyses with linear and logistic regression, no statistically significant differences in mean STAI or the risk of psychological morbidity (GHQ-12 $\geq$ 4) were observed between the control and intervention arms in the random sample. In the analysis of women with recall screening events, there was a statistically significant increased risk of psychological morbidity among women recalled for higher-level screening (adjusted OR 1.28 [95% CI, 1.18 to 1.39]).[99]

The QUEST[92] trial analyzed 549 average-risk women age 30 years or older in the United States to examine the effect of ovarian cancer screening on cancer worry and QoL. Women were randomized to ovarian cancer screening, risk counseling, or a screening/risk counseling combination compared to a usual care-only protocol consisting of annual pelvic examination and routine education by a woman's primary care physician. We report only on results from the screening and usual care control arms of the trial (n = 442). Ovarian cancer screening consisted of alternating CA-125 measurement and TVU every 6 months for a maximum of 4 screening rounds. Overall, women had a high level of education, with 99 percent completing high school and 95 percent attending college. The QUEST[92] study found no statistically significant differences for QoL measured with the SF-36, distress measured with the Impact of Events Scale, or cancer worry measured with a modified Lerman cancer worry scale. The only significant effect observed in participants was a higher level of cancer worry after 2 years among those who had experienced any abnormal test results.[92]

Chapter 4. Discussion

This review considered direct trial evidence of the health benefits and harms of ovarian cancer screening interventions. The known availability of evidence from large trials and previous recommendations against ovarian cancer screening based on trial evidence motivated this focus on the overarching effects of screening on women's health outcomes. The rarity of ovarian cancer necessitated a focus on mortality from ovarian cancer rather than on overall mortality from all-causes because the effects of screening on overall mortality would be minor given that ovarian cancers represent a very small proportion of deaths overall. Because ovarian cancer is rare, large trials are necessary to evaluate effects of screening on ovarian cancer morbidity and mortality in average-risk women.

Summary of Evidence

Since the previous review of this topic mortality results from the large, well-designed UKCTOCS were published. Thus, there were three trials reporting mortality outcomes from ovarian cancer screening. The PLCO and UKCTOCS[86, 87] were designed with statistical power to detect a 30 to 35 percent difference in mortality from this relatively rare but often fatal cancer, and had null findings in primary analyses. The U.K. Pilot trial[93] reported mortality outcomes, but was designed to examine the feasibility of screening and was underpowered to detect a mortality difference. The small QUEST trial[93] evaluated quality of life and psychological effects of ovarian cancer screening. Given evidence that there is no mortality benefit from routine ovarian cancer screening, the harms associated with screening merit extra consideration. For women in the ovarian cancer screening programs evaluated, positive tests and followup can lead to surgery and surgical complications for some women without disease.

Further Discussion of UKCTOCS

Despite a primary null finding from the UKCTOCS on ovarian cancer mortality, the investigators included statistical analyses suggestive of a possible long-term benefit of the CA-125 ROCA screening intervention on ovarian cancer mortality (excluding peritoneal cancers), based on their observation that Kaplan-Meier cumulative morality curves appear to diverge approximately 10 years after randomization. Consistent with best practices,[89] the trialists were transparent in their reporting of protocol-specified versus post hoc exploratory analyses. There are several reasons our review did not focus on these secondary analyses. First, we prioritized analyses with both ovarian and peritoneal cancer included, since their presentation and treatment is not distinct in clinical practice and because they are often difficult to distinguish pathologically. More of the cancers identified in the CA-125 ROCA screening arm of UKCTOCS were coded as peritoneal cancers than in the ultrasound and no screening arms. It is not surprising that excluding these cases that have very high mortality increases the difference in mortality between the CA-125 ROCA and control arm, Nevertheless, excluding peritoneal cancer cases did not alter the null findings of the pre-specified statistical analyses (**Appendix D**).Second, we focused on statistical tests that were specified *a priori* through publication of a

protocol and trial registration. The purpose of prespecification of the analysis plan is to protect against conscious and unconscious selection of statistically significant based on observed patterns in the data and to reduce the risk of Type I hypothesis testing error that occurs when several tests are conducted.[102, 103] In *post hoc* statistical testing, a statistically significant benefit for the CA-125 ROCA intervention was found when peritoneal cancer cases were excluded and a weighted Log Rank test was used to assign greater weight in the survival analysis to later years of the trial (HR 0.78 [95% CI, 0.62 to 0.97]). This report focuses on the primary analysis, as the weighted Log Rank statistical test (used in the PLCO trial) was not prespecified, was undertaken after examining the data, and did not apply multiple test corrections.[102-104] Another secondary analysis of the data that obtained statistically significant findings attempted to remove cases that were prevalent at the outset of the trial, using imputation, modeling and stored CA-125 data when available. Our review focused on intention-to-treat analysis of all participants, since these findings are most robust and applicable to the implementation of a screening program, and its cumulative effects.

Third, the divergence of the trial arms later in the study period are more difficult to attribute to the original randomized condition and screening *per se*, as the longer a study continues, the more opportunities there are for measured and unmeasured differences in the study arms to accrue. There were also substantially fewer women at risk included in the analyses beyond 10 years, because women recruited into the study later have not yet accrued followup time for inclusion in the analysis. Thus, data from the later years of the trial (>10 years) are based on incomplete data and should be cautiously interpreted.

Differential reasons for censoring could lead to some divergence in the ovarian cancer mortality curves as followup times lengthen. In this study, there were no differences across arms in participant followup (censoring) or other causes of death, but there may have been differences between arms and changes over time in the proportion of participants in the trial with two ovaries intact. Those with both ovaries rather than just one, by definition, have higher ovarian cancer risk. In other words, the usual-care screening arm may have had a net surplus of ovaries at risk, despite a similar proportion of women at risk. We calculated the overall proportion of women having an oophorectomy during the trial, based on surgical investigation of screening results (true and false positives) or other indications based on numbers reported for the UKCTOCS. Approximately 4.4 percent of women in the ultrasound arm, 2.3 percent in the CA-125 ROCA arm, and 1.4 percent in the no-screening arm had oophorectomies (commonly bilateral, with or without salpingectomy). Others have suggested that the potential prophylactic effect of ovary and fallopian tube removal might influence the UKCTOCS results, especially in the long term.[105] To date, there is no overall difference in the incidence of ovarian cancer by arm, suggesting that a prophylactic effect is not present, but as more years of followup data are available for more of the enrolled participants, additional analysis of the cumulative cancer incidence rate by study arm can be undertaken. The UKCTOCS team have received grant funding to continue follow up through 2018.[106]

Further Discussion of PLCO

The PLCO was the only U.S.-based study for directly assessing potential net benefits or harms of

screening. The trial protocol consisted of annual transvaginal ultrasound for 4 years and annual CA-125 testing for 6 years. Annual bimanual ovarian palpation by trained examiners was also included during the first 4 years of the trial.[66] Depending on when women entered the study, they received 0 to 4 physical palpation examinations as part of the screening program, consequently 20,872 women in the screening arm received at least one ovarian palpation examination (61%). This screening modality was dropped from the trial, however, because no cancer cases were identified solely on the basis of palpation (i.e., all cancer cases were also positive on CA-125 and/or TVU), and test sensitivity (defined as cancer diagnosed within 1 year of screening positive with a palpable adnexal mass) was very low (5.1%).

Overall, in the PLCO, the ovarian cancer mortality rate was greater in the intervention arm compared with usual care over 13-years of followup, although the difference was not statistically significant.[86] A recently published analysis added up to 6 additional years of post-trial followup mortality data (mean 2.3 years) and did not find evidence of a late-emerging benefit of screening.[107] The post-trial data were obtained through a different, centralized system rather than through the trial screening centers, and upon completion of the trial centralized followup was refused by 16 percent of usual care women and 12 percent of intervention arm participants. Consequently, total followup time was shorter for refusers than for those willing to participate in ongoing surveillance. Overall, however, followup times did not differ across arms with mean followup of approximately 15 years in both groups.[107] The rate ratio moved toward null (RR 1.06 [95% CI, 0.87 to 1.30]) from 1.18 during the trial period. There was also no difference in ovarian cancer specific survival by arm in the trial or its extended followup (p=0.16).

An additional supplemental analysis of PLCO data aimed to determine whether use of the ROCA algorithm on CA-125 measurements collected for the PLCO would have had better performance for identifying ovarian cancer cases compared with the PLCO screening protocol.[108] The analysis employed a best-case scenario assumption biased toward finding a ROCA test benefit over the PLCO protocol. Namely, all cancers in the trial that would have had a positive ROCA screening test occurring earlier than a positive screening test with the PLCO protocol were assumed to have avoided mortality from ovarian cancer. Modeling with PLCO data suggested that application of the ROCA algorithm used in the UKCTOCS would have led to earlier diagnosis of cancer in 32 percent of cases that were detected using CA125 screening using a single cutoff.[108] This analysis obtained a mortality relative risk of 0.90 (95% CI, 0.69 to 1.17), and the authors concluded that even under the most lenient assumptions, the ROCA algorithm would not necessarily have resulted in a beneficial trial finding.

Another recent secondary analysis of PLCO participants with a family history of breast or ovarian cancer found a non-significant trend towards diagnosis of stage I or II cancers in the screened arm compared with the usual care arm (29% versus 17%; p=0.085)[109] and improved survival in these patients with ovarian cancer detected by screening compared to usual care; however, this apparent improvement in survival did not result in improved ovarian cancer mortality.[109]

The control condition was described as “usual care” in the U.S. PLCO and as “no screening” in the U.K. trials. If usual care included any practices that might affect ovarian cancer detection and treatment, this could potentially reduce differences between the study arms in the PLCO.

Surveys have found that a majority of U.S. primary care and reproductive specialty clinicians conduct bimanual pelvic examinations as part of their routine gynecological care for women, believing it to be an effective way to screen for ovarian cancer.[65, 110] During the early years of the PLCO, the screening protocol included ovarian palpation with bimanual pelvic examinations, but this element was dropped from the intervention protocol 5 years into the trial. Estimates of the test performance of the bimanual examination derived from the PLCO and systematic reviews of the effectiveness of routine pelvic examinations[111] have found limited evidence on its effectiveness, and have brought to light its poor accuracy. Thus, it is unlikely that ovarian palpation in the screening or control arm of the PLCO would influence the results observed. Essentially, women in both arms of the PLCO likely received pelvic examinations with ovarian palpation over the course of the study, and the CA-125 and TVU screening intervention can be validly compared against usual care without routine CA-125 and TVU screening. Overall rates of TVU and CA-125 testing contamination in the control arm were similar for the PLCO and U.K.-based studies, however, suggesting that differences in the control condition did not contribute to widely divergent practices in the control arms.

Implications of Stage Shift and Treatment Findings in the Absence of a Mortality Benefit

As a contextual question in this review, we examined included studies for evidence of a cancer stage or type shift We focused the evaluation of stage shift on comparisons in the trial arms between women diagnosed with localized disease (stage I) and those with regional or distant disease (stages II-IV). These comparisons are relevant because of the higher survival rates associated with disease diagnosed at the localized stage and clinical differences in treatment strategies between stage I and higher-stage ovarian cancer (i.e., need for adjuvant radiation therapy).[1] Patients with stage II ovarian cancer have high recurrence rates. As a result, in 2009 the Gynecologic Oncology Group has recommended that stage II patients be included in trials that assess treatments for advanced-stage disease.[1] Tests for differences in proportions were conducted in Stata.

Detection of a higher proportion of localized cancers in the screening arms compared with control arms was reported in the two large trials. In the UKCTOCS[87] a statistically significant ($p<0.005$) greater proportion of cases was identified at the localized stage (stage I) in the CA-125 ROCA (36%) and ultrasound (31%) arms than in the control arm (23%). The overall differences by arm and stage were also statistically significant when comparing localized and regional cancers (stages I and II) to more advanced stages (stages III and IV). Differences between the CA-125 ROCA and ultrasound arms were not statistically significant.[87] In the PLCO[86] there was not a statistically significant difference in the proportion of cases identified at the localized stage in the intervention versus usual care group (15 versus 10%, $p =0.08$). Comparisons by stage and arm also were not statistically different when comparing localized and regional cancer cases to more advanced cancers.

In addition, there were no differences in treatments by study arm in the PLCO; 81 percent in the intervention group received surgery plus systemic therapy, compared with 80 percent in the usual care group.[86] Treatment outcomes for participants in the UKCTOCS[87] have not yet been

published. While there is some evidence of a stage shift for the CA-125 ROCA and ultrasound intervention arms in the UKCTOCS, this shift did not confer a statistically significant mortality benefit.

Only the UKCTOCS examined the differences of detection on cancer type and found difference in the detection of more aggressive type II cancers with either screening intervention.[87] More cancers classified as type II were identified in the screening arms (60% of all cases in TVU and CA-125 ROCA arm versus 64% in the control arm), and more non-epithelial and borderline types were found in the screening arms. The borderline and non-epithelial types are more likely to be early stage cancers, and have high rates of survival.[112] Thus, finding more indolent disease with screening may have had limited impact on ovarian cancer survival, even though it appears to contribute to an observed shift in disease stage. Among invasive epithelial and peritoneal cancer cases found, however, the CA-125 ROCA screening test appeared to identify slightly more cases at an earlier stage. Even stage I cancers, however, in some type II high grade epithelial carcinomas may be associated with microscopic metastases, as cancer cells can be present in ascites (stage Ic).[2, 4, 5, 9]

The absence of a mortality benefit in these large, well-conducted trials has generated a theory that late stage disease grows so rapidly that it cannot be identified at an earlier stage. The stage shift in UKCTOCS trial would seem to counter this, but the lack of mortality benefit may suggest that these "early stage" tumors detected early are more aggressive tumor phenotypes that would not have improved survival no matter when they were identified. Recent work to refine the distinctions among ovarian cancer molecular, pathological, and clinical characteristics highlight this point in noting that survival differences are more likely attributable to type than to stage at diagnosis, with the most common type II cancers being particularly lethal regardless of stage, likely owing to microscopic lesions that are not detectable before significant spread has occurred.[9]

Discussion of Harms

The UKCTOCS employed a more nuanced approach to CA-125 testing and triage by using an algorithm that incorporates CA-125-level trajectories, assigning three levels of risk to direct surveillance and triage tests. This was aimed at reducing rates of surgical investigation, and indeed surgery rates were lower in the CA-125 ROCA arm than in the ultrasound-only arm of the trial. Accordingly, false positive surgery rates in the CA-125 ROCA arm of the UKCTOCS were markedly lower than in the PLCO (1% versus 3%).

The surgical complication rates differed considerably for the PLCO and UKCTOCS, with 15 percent of women who underwent false positive surgery experiencing a major complication in the PLCO and just over 3 percent having a major complication from false positive surgery in the UKCTOCS. Differences in the study settings could account in part for this difference, as diagnostic testing in the PLCO was conducted through referrals to women's routine sources of care, and not necessarily specialized tertiary care settings. In contrast, in the U.K. all women referred for diagnostic testing were seen at National Health Services tertiary care surgical centers. It is unclear whether the complication rates observed in the PLCO would be observed in

current U.S. community surgical practices for women referred for diagnostic testing from primary care. Current U.S. data on the complication rates for diagnostic oophorectomy (alone) are not available, but it is likely that rates vary by setting, region, and clinician characteristics.[113] Regardless of the complication rates, high rates of surgery and removal of women's ovary or ovaries in the absence of disease occurred in both trials, although rates of surgery were lowest in the CA-125 ROCA screening intervention in the UKCTOCS trial.

False positive surgical investigations in the included trials were reported to often include bilateral salpingo-oophorectomy (BSO), based on common practice for the investigation of suspected ovarian cancer.[28] Given that these screening interventions were undertaken in healthy women, potential harms of unnecessary removal of the ovaries in postmenopausal women deserves scrutiny. A recent systematic review evaluated the general health consequences of BSO at the time of hysterectomy for benign indications.[114] Health consequences for women undergoing surgical investigation for a false positive ovarian cancer screen receiving BSO would likely be comparable. Although evidence was somewhat limited, the review found reductions in ovarian cancer and in rates of reoperation for women who underwent BSO, but particularly for women younger than 45 years old. There was also evidence of potential adverse effects on cardiovascular health and all-cause mortality. Sexual function may also be negatively impacted by BSO conducted at the time of benign hysterectomy.[114] Thus, the removal of ovaries and or fallopian tubes at the time of a surgical investigation for a false positive screening test result may have downstream harms beyond those owing to the direct effects of surgery on health outcomes. Evidence on the effects of BSO among older postmenopausal women similar to those included in this trial is limited, and firm conclusions about adverse or beneficial health or social effects are not possible.

Limitations of the Review

Although a body of evidence on the test performance of various screening strategies exists, the most promising approaches using ultrasound and CA-125 have been assessed in trials. Our review did not consider observational evidence, where some tools have appeared promising in early investigations.

Given the rarity of ovarian cancer, and the invasiveness of diagnostic surgery for positive screening results, the mortality reduction from screening relative to an unscreened group is key evidence for this condition, as it summarizes the net effect of screening, detection, and treatment.[115] An effective ovarian cancer-screening program among asymptomatic average-risk women would be hypothesized to save lives through lower rates of death from ovarian cancer. Observation of a cancer stage shift toward more localized cancers may lead to less morbid treatments and could underlie an observed screening mortality benefit, but stage shifts do not necessarily confer a mortality benefit. Namely, a screening test might identify cancers that would not have progressed or earlier treatment might not sufficiently change the survival rates women to make a difference relative to an unscreened group. Even in the absence of an organized screening program, asymptomatic ovarian cancers may be detected opportunistically. Evidence from randomized trials of ovarian cancer-screening programs that report mortality outcomes can establish whether specific screening protocols result in better health outcomes (e.g., reduced

mortality) than usual care or the absence of the screening program. This direct evidence is available from two large trials, and unfortunately neither provides evidence of a screening benefit with any of the screening protocols tested.

Given the low incidence of ovarian cancer, very large trials are necessary to determine whether the benefits of a screening program outweigh the harms of diagnostic testing, which for ovarian cancer necessarily involves surgery and ovarian removal. We are confident that our review identified all relevant trials with ovarian cancer-mortality outcomes reported. Two additional trials that did not meet our inclusion criteria on the basis of study design and outcome reporting, but enrolled large samples of women to ovarian cancer screening would not have changed our findings had they been included.

The Shizuoka Cohort Study of Ovarian Cancer Screening and Shizuoka Cancer Registry (SCSOCS trial) randomized asymptomatic postmenopausal women in Shizuoka, Japan, to screening using ultrasonography and CA-125 (with a cutoff of 35 U/ml) (n= 41, 688) or followup without screening (n=40,799).[116] Screenings were repeated yearly for an average of 5.4 screens and a mean followup of 9.2 years. Information on the impact of screening on ovarian cancer diagnosis was published in 2008, with no significant difference between the number of women with ovarian cancer detected between the screening and control groups. Differences in the percent of patients detected with stage I cancer were also not statistically significant (63% versus 38%, p=0.23). Mortality data have not been published from this trial, and it is unclear if additional analyses are planned.[116] The SCOSCS was not included in the results of this review because health outcomes have not been reported for this trial.

The University of Kentucky Ovarian Cancer Screening Trial was initiated in 1987 to assess the use of annual transvaginal ultrasound to detect ovarian cancer in asymptomatic women aged 50 or older and women aged 25 or older with a family history of ovarian cancer. [117] The study was a controlled trial, but did not randomize women to a control condition, instead comparing the screened cohort to a cohort of women with ovarian cancer outcomes reported in the Kentucky Tumor Registry. Data published on the effect of screening TVU on over 37,000 women from 1987 to 2011 reported that in the screening cohort 47 percent of cancers were detected at stage I and 70 percent were detected with stage I or II disease. In contrast, only 27 percent of those entered into the Kentucky Tumor Registry during the same time period had stage I or II disease ($p<0.01$). The 5-year disease-free survival rate for those cancers detected by screening was 85 percent compared with 54 percent of unscreened women treated at the same cancer center using the same surgical and chemotherapeutic protocols ($p<0.001$).[117] This study also reported fewer surgical complications (10% of subjects) compared with the PLCO.[118] Our review did not include this evidence because the screening and comparison cohorts included both average-risk and high-risk women, and the participants were not randomly assigned to study groups. Further analyses of this investigation have not been reported, and there are limits with regard to conclusions that can be drawn about the effectiveness of a TVU screening program based on a cohort comparison study design.

The scope of this review was limited to the type of evidence that would be necessary to inform a change in clinical practice in accordance with USPSTF standards. While some topics evaluate the effectiveness of screening through an indirect pathway logic model, considering the

performance of a screening test separately from the effectiveness of treatment. Evidence that tests the effect of screening compared with the absence of screening on intended health outcomes in a randomized design does not require as much inference across heterogeneous bodies of evidence. Nevertheless, trial evidence can have limitations in terms of generalizability and applicability to usual care. The PLCO[86] is more applicable to a U.S. setting than the UKCTOCS,[87] since the PLCO referred women to usual care settings. The low surgical complication rates from surgery seen in the UKCTOCS[87], for example, may have been due to the receipt of care in tertiary care centers which is standard in the U.K. health system. Similarly, screening tests offered through a trial might be more accurate than screening performance in routine care settings, or surgical investigations might be more common in the absence of trial protocols.

Future Research Needs

Given null findings from two major, well-powered trials, future research may focus on identifying women at elevated risk of ovarian cancer that could be found to experience benefits of screening or prophylactic intervention. More work is needed, however, to develop approaches for assessing family history and ovarian cancer risk in primary care and to optimize women's use of genetic counselors. Research is also needed to identify new markers with greater sensitivity and specificity for detection of ovarian cancer in average-risk women. In 2016, the IOM recommended additional research should focus on the development and assessment of early detection strategies that extend beyond current imaging modalities and biomarkers and reflect the pathobiology of each ovarian cancer subtype.[2]

The appearance of diverging cumulative mortality curves in the later years of the UKCTOCS has been a focus of the study investigators and critical commentaries. Given the absence of any effective screening modality to reduce mortality from ovarian cancer, any hint at a possible benefit merits close attention. As the UKCTOCS investigators point out, a few more years of data from the trial are needed to accrue followup data on women who entered the trial later in the enrollment period so that the complete findings are included in the later years of the analysis. Nevertheless, questions can be asked in the meantime about the mechanism that might underlie a screening intervention benefit for ovarian cancer occurring several years after the screening program ended. Given the natural history of ovarian cancer, it is unclear how a screening intervention aimed at identifying ovarian cancer and intervening at a more treatable stage would have a delayed effect. One possible explanation is that the screening activities resulted in the removal of the abnormal appearing but nonmalignant ovaries and fallopian tubes of women, and some of these otherwise might have gone on to develop ovarian cancer in later years. Given the relatively high false positive surgery rates seen in this trial, it is possible that prophylactic removal of selected women's ovaries and fallopian tubes would have effects on the later divergence of the cumulative mortality curves. A sensitivity analysis of the trial data using ovaries at risk, rather than women at risk as the dominator, might shed light on this potential effect on the trial results. The absence of an overall difference in ovarian cancer incidence suggests that the higher rate of oophorectomy may not be influential, but analyses examining the cumulative ovarian cancer incidence over the course of the trial and with more followup data could be informative.

More detailed data on the surgeries following screening would shed further light on possible interpretations of the diverging cumulative risk curves highlighted by the study authors. While rates of ovarian cancer have been found to be lower among women opting for removal at the time of hysterectomy for benign pathology or elective reasons,[49] reductions in the risk of rare ovarian cancers have to be weighed against possible negative effects of oophorectomy for other conditions, and risks associated with surgery.[114, 119, 120]

Evidence of health risks associated with removal of the ovaries, although limited among post-menopausal women, includes negative consequences for cardiovascular health, sexual function, and some mental health outcomes.[114] Given growing recognition that many ovarian cancers originate in the fallopian tubes, prophylactic salpingectomy with ovarian conservation at the time of surgery for other indications is viewed as a potentially promising preventive strategy for women undergoing pelvic surgery for other reasons. Overall, in the United States, rates of opportunistic salpingectomy are increasing, although opportunistic BSO is far more common.[121] Nevertheless, ACOG does not fully endorse routine salpingectomy at the time of benign indication hysterectomy or sterilization until rigorous observational or trial evidence on this intervention is available.[47] Given that preservation of the ovaries is a more conservative practice, this practice may disseminate more readily. Data from a large community-based health system in Northern California reported an increase from 15 percent to 72 percent between 2011 and 2014 in the practice of salpingectomy at the time of elective hysterectomy for benign indications following the distribution of resources related to the potential benefits of the practice.[122]

Differences in the oophorectomy rates were also estimated in the PLCO, based on a supplemental survey following the screening period (66% of participants responded).[86, 96] More women in the intervention arm reported an oophorectomy (7.7% versus 5.8%, RR 1.33 [95% CI, 1.24 to 1.43]). The PLCO did not find a long-term benefit of screening; the cumulative mortality effect estimate was in the direction of harms rather than benefits of screening. In the longer-term followup data from the trial, however, the intervention effect estimate moved closer to null.[107]

We identified no ongoing randomized trials of ovarian cancer screening using new screening tools. While some tools in development may hold promise for the future (e.g., microRNA),[2] currently there are no new screening tools (i.e., biomarkers, instruments) exhibiting levels of test performance beyond what is observed for the screening tools evaluated in trials.

The UKCTOCS trialists are engaged in efforts to improve upon the ROCA algorithm, adding other protein markers along with CA-125 to new prediction models derived using data from the UKCTOCS data. These models would require further validation and testing to ascertain whether they truly represent improvements on the ROCA algorithm that would potentially attain clinical benefits for ovarian cancer detection and treatment. In any case, 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 in prediction models.[123]

Methods for identifying women at high-risk for ovarian cancer may help to direct preventive interventions. In 2016, a report from the Institute of Medicine recommended that research focus on developing and validating dynamic risk assessment tools for identifying those at high risk of cancer, including increasing rates of genetic counseling, and to exam the risk-benefit balance of

nonsurgical and surgical prevention strategies in these populations.[2]

Conclusion

Since the previous review, results from a large trial conducted in the United Kingdom were published. Ovarian cancer mortality did not differ between control and intervention screening conditions in any of the included trials, including two good-quality studies with adequate power to detect differences. Harms of screening include surgery resulting from a false positive. These surgeries often result in the removal of one or both ovaries and/or fallopian tubes, and can lead to major surgical complications. Reports from the UKCTOCS of a potential delayed effect of screening on ovarian cancer mortality require further follow data to evaluate, but the causal mechanism for a delayed screening effect is unclear. Major trials of promising ovarian cancer screening tools have null findings to date among healthy average-risk women, and there are considerable harms associated with screening. Further analysis of existing trials and research on new biomarkers, new risk-assessment tools, and trials of prophylactic interventions may ultimately be found to be useful in reducing ovarian cancer mortality and will need to be weighed against known screening harms.

References

1. National Cancer Institute. Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®)–Health Professional Version. https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq. Accessed November 17, 2016. PMID: None.
2. Institute of Medicine, Committee on the State of the Science in Ovarian Cancer Research, Board on Health Care Services, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. 2016. PMID: 27253000. http://dx.doi.org/10.17226/21841
3. National Cancer Institute. Staging. https://www.cancer.gov/about-cancer/diagnosis-staging/staging. Accessed November 2, 2016. PMID: None.
4. Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014;124(1):1-5. PMID: 24219974. http://dx.doi.org/10.1016/j.ijgo.2013.10.001
5. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. Lancet. 2014;384(9951):1376-88. PMID: 24767708. http://dx.doi.org/10.1016/S0140-6736(13)62146-7
6. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975–2012. Bethesda, MD: National Cancer Institute. 2015. PMID: None.
7. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2013 Incidence and Mortality Web-based Report*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2016. Available at www.cdc.gov/uscs. PMID: None.
8. National Cancer Institute. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed November 2, 2016. PMID: None.
9. Kurman RJ, Shih Ie M. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. Am J Pathol. 2016;186(4):733-47. PMID: 27012190. http://dx.doi.org/10.1016/j.ajpath.2015.11.011
10. Koshiyama M, Matsumura N, Konishi I. Recent concepts of ovarian carcinogenesis: type I and type II. Biomed Res Int. 2014;2014:934261. PMID: 24868556. http://dx.doi.org/http://dx.doi.org/10.1155/2014/934261
11. Reade CJ, McVey RM, Tone AA, et al. The fallopian tube as the origin of high grade serous ovarian cancer: review of a paradigm shift. J Obstet Gynaecol Can. 2014;36(2):133-40. PMID: 24518912. http://dx.doi.org/10.1016/S1701-2163(15)30659-9
12. Kurman RJ, Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathol. 2011;42(7):918-31. PMID: 21683865. http://dx.doi.org/10.1016/j.humpath.2011.03.003
13. North American Association of Central Cancer Registries. Average-annual age-adjusted cancer incidence rates by race/ethnicity, sex, and registry for selected sites. http://www.naaccr.org/DataandPublications/CINAPubs.aspx. Accessed November 2, 2016. PMID: None.
14. Permuth-Wey J, Besharat A, Sellers T. Epidemiology of ovarian cancer: An update. In: Advances in diagnosis and management of ovarian cancer. Farghaly SA, editor. New York: Springer Science and Business Media; 2014. PMID: None.

15. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. J Clin Oncol. 2016;34(24):2888-98. PMID: 27325851. http://dx.doi.org/10.1200/JCO.2016.66.8178
16. Shulman LP, Dungan JS. Cancer genetics: risks and mechanisms of cancer in women with inherited susceptibility to epithelial ovarian cancer. Cancer Treat Res. 2010;156:69-85. PMID: 20811826. http://dx.doi.org/10.1007/978-1-4419-6518-9_6
17. Lu KH, Daniels M. Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. Fam Cancer. 2013;12(2):273-7. PMID: 23765559. http://dx.doi.org/10.1007/s10689-013-9664-5
18. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol. 2011;12(1):49-55. PMID: 21145788. http://dx.doi.org/10.1016/S1470-2045(10)70265-5
19. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA Cancer J Clin. 2006;56(4):213-25. PMID: 16870997.
20. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70-87. PMID: 25394175. http://dx.doi.org/10.1038/gim.2014.147
21. Song H, Ramus SJ, Tyrer J, et al. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet. 2009;41(9):996-1000. PMID: 19648919. http://dx.doi.org/10.1038/ng.424
22. Pharoah PD, Tsai YY, Ramus SJ, et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013;45(4):362-70, 70e1-2. PMID: 23535730. http://dx.doi.org/10.1038/ng.2564
23. Permuth-Wey J, Lawrenson K, Shen HC, et al. Identification and molecular characterization of a new ovarian cancer susceptibility locus at 17q21.31. Nat Commun. 2013;4:1627. PMID: 23535648. http://dx.doi.org/10.1038/ncomms2613
24. Kuchenbaecker KB, Ramus SJ, Tyrer J, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet. 2015;47(2):164-71. PMID: 25581431. http://dx.doi.org/10.1038/ng.3185
25. Bolton KL, Tyrer J, Song H, et al. Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet. 2010;42(10):880-4. PMID: 20852633. http://dx.doi.org/10.1038/ng.666
26. Bojesen SE, Pooley KA, Johnatty SE, et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet. 2013;45(4):371-84, 84e1-2. PMID: 23535731. http://dx.doi.org/10.1038/ng.2566
27. National Institute for Health and Care Excellence (NICE). Clinical guideline [CG164]: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2013. PMID: None.
28. Daly MB, Pilarski R, Axilbund JE, et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015. J Natl Compr Canc Netw. 2016;14(2):153-62. PMID: 26850485.

29. Moyer VA, Force USPST. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160(4):271-81. PMID: 24366376. http://dx.doi.org/10.7326/M13-2747
30. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303-14. PMID: 18294997. http://dx.doi.org/10.1016/S0140-6736(08)60167-1
31. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol. 1992;136(10):1184-203. PMID: 1476141.
32. Fortner RT, Ose J, Merritt MA, et al. Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: Results from the EPIC cohort. Int J Cancer. 2015;137(5):1196-208. PMID: 25656413. http://dx.doi.org/10.1002/ijc.29471
33. Gates MA, Rosner BA, Hecht JL, et al. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 2010;171(1):45-53. PMID: 19910378. http://dx.doi.org/10.1093/aje/kwp314
34. Merritt MA, De Pari M, Vitonis AF, et al. Reproductive characteristics in relation to ovarian cancer risk by histologic pathways. Hum Reprod. 2013;28(5):1406-17. PMID: 23315066. http://dx.doi.org/10.1093/humrep/des466
35. Yang HP, Trabert B, Murphy MA, et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. Int J Cancer. 2012;131(4):938-48. PMID: 21960414. http://dx.doi.org/10.1002/ijc.26469
36. Setiawan VW, Yang HP, Pike MC, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31(20):2607-18. PMID: 23733771. http://dx.doi.org/10.1200/JCO.2012.48.2596
37. Hartge P, Whittemore AS, Itnyre J, et al. Rates and risks of ovarian cancer in subgroups of white women in the United States. The Collaborative Ovarian Cancer Group. Obstet Gynecol. 1994;84(5):760-4. PMID: 7936508.
38. Rosner BA, Colditz GA, Webb PM, et al. Mathematical models of ovarian cancer incidence. Epidemiology. 2005;16(4):508-15. PMID: 15951669.
39. Pfeiffer RM, Park Y, Kreimer AR, et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. PLoS Med. 2013;10(7):e1001492. PMID: 23935463. http://dx.doi.org/10.1371/journal.pmed.1001492
40. Li K, Husing A, Fortner RT, et al. An epidemiologic risk prediction model for ovarian cancer in Europe: the EPIC study. Br J Cancer. 2015;112(7):1257-65. PMID: 25742479. http://dx.doi.org/10.1038/bjc.2015.22
41. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967-75. PMID: 20810374. http://dx.doi.org/10.1001/jama.2010.1237

42. Jacoby VL, Grady D, Wactawski-Wende J, et al. Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. Arch Intern Med. 2011;171(8):760-8. PMID: 21518944. http://dx.doi.org/10.1001/archinternmed.2011.121
43. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009;113(5):1027-37. PMID: 19384117. http://dx.doi.org/10.1097/AOG.0b013e3181a11c64
44. Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32(15):1547-53. PMID: 24567435. http://dx.doi.org/10.1200/JCO.2013.53.2820
45. Falconer H, Yin L, Gronberg H, et al. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 2015;107(2). PMID: 25628372 http://dx.doi.org/10.1093/jnci/dju410
46. Guldberg R, Wehberg S, Skovlund CW, et al. Salpingectomy as standard at hysterectomy? A Danish cohort study, 1977-2010. BMJ Open. 2013;3(6). PMID: 23794553 http://dx.doi.org/10.1136/bmjopen-2013-002845
47. Ammerican College on Obstetricians and Gynecologists (ACOG) Committee on Gynecologic Practice. Committee opinion no. 620: Salpingectomy for ovarian cancer prevention. Obstet Gynecol. 2015;125(1):279-81. PMID: 25560145. http://dx.doi.org/10.1097/01.AOG.0000459871.88564.09
48. Society of Gynecologic Oncology (SGO). SGO clinical practice statement: Salpingectomy for ovarian cancer prevention. https://www.sgo.org/clinical-practice/guidelines/sgo-clinical-practice-statement-salpingectomy-for-ovarian-cancer-prevention. Accessed November 23, 2016. PMID: None.
49. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. J Ovarian Res. 2012;5(1):13. PMID: 22587442. http://dx.doi.org/10.1186/1757-2215-5-13
50. Walker JL, Powell CB, Chen LM, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer. 2015;121(13):2108-20. PMID: 25820366. http://dx.doi.org/10.1002/cncr.29321
51. Havrilesky LJ, Gierisch JM, Moorman PG, et al. Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer. Evidence Report/Technology Assessment No. 212. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.). AHRQ Publication No 13-E002-EF PMID: None.
52. Bristow RE, Chang J, Ziogas A, et al. Adherence to treatment guidelines for ovarian cancer as a measure of quality care. Obstet Gynecol. 2013;121(6):1226-34. PMID: 23812456. http://dx.doi.org/10.1097/AOG.0b013e3182922a17
53. Bristow RE, Chang J, Ziogas A, et al. High-volume ovarian cancer care: survival impact and disparities in access for advanced-stage disease. Gynecologic oncology. 2014;132(2):403-10. PMID: 24361578. http://dx.doi.org/10.1016/j.ygyno.2013.12.017
54. Chan JK, Kapp DS, Shin JY, et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. Obstet Gynecol. 2007;109(6):1342-50. PMID: 17540806. http://dx.doi.org/10.1097/01.AOG.0000265207.27755.28

55. Goff BA, Mandel LS, Melancon CH, et al. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 2004;291(22):2705-12. PMID: 15187051. http://dx.doi.org/10.1001/jama.291.22.2705
56. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer. 2007;109(2):221-7. PMID: 17154394. http://dx.doi.org/10.1002/cncr.22371
57. Ebell MH, Culp MB, Radke TJ. A Systematic Review of Symptoms for the Diagnosis of Ovarian Cancer. Am J Prev Med. 2016;50(3):384-94. PMID: 26541098. http://dx.doi.org/10.1016/j.amepre.2015.09.023
58. Bast RC, Jr., Skates S, Lokshin A, et al. Differential diagnosis of a pelvic mass: improved algorithms and novel biomarkers. International Journal of Gynecological Cancer. 2012;22 Suppl 1:S5-8. http://dx.doi.org/http://dx.doi.org/10.1097/IGC.0b013e318251c97d
59. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. British journal of obstetrics and gynaecology. 1990;97(10):922-9. PMID: 2223684.
60. Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecologic oncology. 2009;112(1):40-6. http://dx.doi.org/http://dx.doi.org/10.1016/j.ygyno.2008.08.031
61. Skates SJ, Xu FJ, Yu YH, et al. Toward an optimal algorithm for ovarian cancer screening with longitudinal tumor markers. Cancer. 1995;76(10 Suppl):2004-10. PMID: 8634992.
62. Manegold-Brauer G, Bellin AK, Tercanli S, et al. The special role of ultrasound for screening, staging and surveillance of malignant ovarian tumors: distinction from other methods of diagnostic imaging. Arch Gynecol Obstet. 2014;289(3):491-8. PMID: 24253338. http://dx.doi.org/10.1007/s00404-013-3081-8
63. Woolas RP, Xu FJ, Jacobs IJ, et al. Elevation of multiple serum markers in patients with stage I ovarian cancer. J Natl Cancer Inst. 1993;85(21):1748-51. PMID: 8411259.
64. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol. 2009;10(4):327-40. PMID: 19282241. http://dx.doi.org/10.1016/S1470-2045(09)70026-9
65. Stormo AR, Cooper CP, Hawkins NA, et al. Physician characteristics and beliefs associated with use of pelvic examinations in asymptomatic women. Prev Med. 2012;54(6):415-21. PMID: 22484240. http://dx.doi.org/10.1016/j.ypmed.2012.03.012
66. Doroudi M, Kramer B, Pinsky P. The bimanual ovarian palpation examination in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: Performance and complications. J Med Screen. 2016;0(0):1-3. PMID: 27903809. http://dx.doi.org/10.1177/0969141316680381
67. Qaseem A, Humphrey LL, Harris R, et al. Screening pelvic examination in adult women: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161(1):67-72. PMID: 24979451. http://dx.doi.org/10.7326/M14-0701

68. US Preventive Services Task Force. Screening for Gynecologic Conditions With Pelvic Examination: US Preventive Services Task Force Recommendation Statement. JAMA. 2017;317(9):947-53. PMID: None. http://dx.doi.org/10.1001/jama.2017.0807
69. American College of Obstetricians and Gynecologists (ACOG). The role of the obstetrician–gynecologist in the early detection of epithelial ovarian cancer. Committee Opinion No. 477. Obstet Gynecol. 2011;117:742-6. PMID: 21343791. http://dx.doi.org/10.1097/AOG.0b013e31821477db
70. Moyer VA, U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement.[Summary for patients in Ann Intern Med. 2012 Dec 18;157(12):I-56; PMID: 23362519]. Ann Intern Med. 2012;157(12):900-4. PMID: 22964825. http://dx.doi.org/10.7326/0003-4819-157-11-201212040-00539
71. American Academy of Family Physicians. Clinical Preventive Service Recommendation: Ovarian Cancer. http://www.aafp.org/patient-care/clinical-recommendations/all/ovarian-cancer.html. Accessed November 17, 2016. PMID: None.
72. Smith RA, Brooks D, Cokkinides V, et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin. 2013;63(2):88-105. PMID: 23378235. http://dx.doi.org/10.3322/caac.21174
73. Pandharipande PV, Harvey HB, Javitt MC, et al. ACR Appropriateness Criteria® ovarian cancer screening. 2012. PMID: None.
74. Baldwin LM, Trivers KF, Matthews B, et al. Vignette-based study of ovarian cancer screening: do U.S. physicians report adhering to evidence-based recommendations?.[Erratum appears in Ann Intern Med. 2012 Jun 19;156(12):908]. Ann Intern Med. 2012;156(3):182-94. PMID: 22312138. http://dx.doi.org/10.7326/0003-4819-156-3-201202070-00006
75. Baldwin LM, Trivers KF, Andrilla CH, et al. Accuracy of ovarian and colon cancer risk assessments by U.S. physicians. J Gen Intern Med. 2014;29(5):741-9. PMID: 24519100. http://dx.doi.org/10.1007/s11606-014-2768-2
76. U.S. Food and Drug Administration. The FDA recommends against using screening tests for ovarian cancer screening: FDA Safety Communication. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm519413.htm. Accessed December 30, 2016. PMID: None.
77. Abcodia. Abcodia Statement on the ROCA Test for Ovarian Cancer Screening. https://www.rocatest.com/about-us/news-events/news-item/abcodia-statement-roca-test-ovarian-cancer-screening/. Accessed December 30, 2016. PMID: None.
78. Danforth KN, Im TM, Whitlock EP. Addendum to Screening for Ovarian Cancer: Evidence Update for the U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. AHRQ Publication No. 12-05165-EF4 Rockville, MD: Agency for Healthcare Research and Quality: April 2012. PMID: None.
79. Barton M, Lin K. Screening for Ovarian Cancer: Evidence Update for the U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. AHRQ publication no. 12-05165-EF3. Rockville, MD: Agency for Healthcare Research and Quality: April 2012. PMID: None.

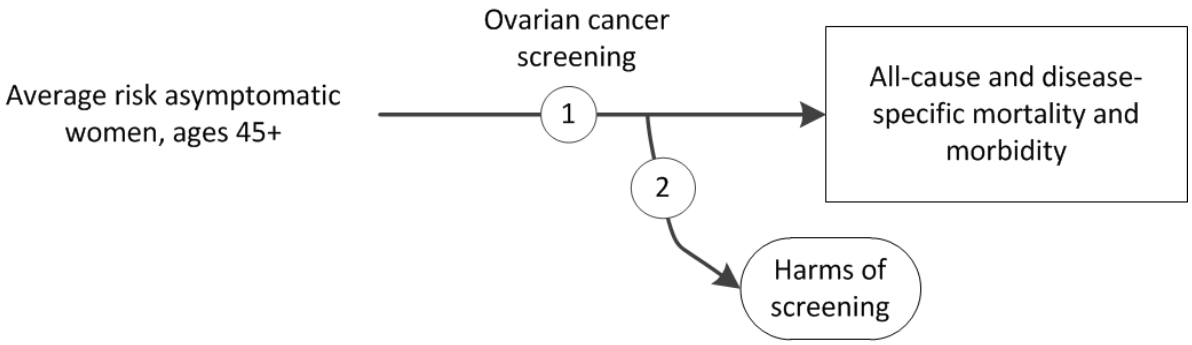
80. Nelson H, Westhoff C, Piepert J, et al. Screening for Ovarian Cancer: Brief Evidence Update. AHRQ Publication No. 04-0542-B. Rockville, MD: Agency for Healthcare Research and Quality: May 2004. PMID: None.
81. Kaiser Permanente Southern California. Ovarian Cancer Screening Clinical Practice Guideline. Recommendations and Rationale. December 2014. PMID: None.
82. Reade CJ, Riva JJ, Busse JW, et al. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. Gynecologic oncology. 2013;130(3):674-81. http://dx.doi.org/http://dx.doi.org/10.1016/j.ygyno.2013.06.029
83. Wallace BC, Small K, Brodley CE, et al., editors. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. 2nd ACM SIGHIT International Health Informatics Symposium 2012. PMID: None.
84. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229. http://dx.doi.org/10.1016/S0749-3797(01)00261-6
85. Daya D, Cheung A, Khunamornpong S, et al. Tumors of the peritoneum: epithelial tumors of Müllerian type. in: RJ Kurman, ML Carcangiu, CS Herrington, RH Young (Eds.) In: WHO classification of tumors of female reproductive organs. 4th edn: International Agency for Research on Cancer, Lyon; 2014. p. 92-3. PMID: None.
86. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011;305(22):2295-303. PMID: 21642681. http://dx.doi.org/10.1001/jama.2011.766
87. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2015. PMID: 26707054. http://dx.doi.org/10.1016/s0140-6736(15)01224-6
88. Menon U, Kalsi JK, Gentry-Maharaj A, et al. Reply to P.F. Pinsky, C.P. Crum, and M.W. McIntosh et al. J Clin Oncol. 2016;34(2):201-2. PMID: 26573079. http://dx.doi.org/10.1200/JCO.2015.64.1365
89. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32. PMID: 20335313. http://dx.doi.org/10.7326/0003-4819-152-11-201006010-00232
90. Berkman ND, Santaguida PL, Viswanathan M, et al. In: The Empirical Evidence of Bias in Trials Measuring Treatment Differences. Rockville (MD)2014. PMID: 25392898.
91. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. PMID: 15205295. http://dx.doi.org/10.1136/bmj.328.7454.1490
92. Andersen MR, Drescher CW, Zheng Y, et al. Changes in cancer worry associated with participation in ovarian cancer screening. Psychooncology. 2007;16(9):814-20. PMID: 17225260. http://dx.doi.org/10.1002/pon.1151
93. Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. Lancet. 1999;353(9160):1207-10. PMID: 10217079. http://dx.doi.org/10.1016/s0140-6736(98)10261-1
94. Jacobs I, Davies AP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. BMJ. 1993;306(6884):1030-4. PMID: 8490497. http://dx.doi.org/10.1136/bmj.306.6884.1030

95. Gren L, Broski K, Childs J, et al. Recruitment methods employed in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Clin. 2009;6(1):52-9. PMID: 19254935. http://dx.doi.org/http://dx.doi.org/10.1177/1740774508100974
96. Buys SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 2005;193(5):1630-9. PMID: 16260202. http://dx.doi.org/10.1016/j.ajog.2005.05.005
97. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Controlled clinical trials. 2000;21(6 Suppl):273s-309s. PMID: 11189684.
98. Menon U, Ryan A, Kalsi J, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015;33(18):2062-71. PMID: 25964255. http://dx.doi.org/10.1200/JCO.2014.59.4945
99. Barrett J, Jenkins V, Farewell V, et al. Psychological morbidity associated with ovarian cancer screening: results from more than 23,000 women in the randomised trial of ovarian cancer screening (UKCTOCS). BJOG. 2014;121(9):1071-9. PMID: 24865441. http://dx.doi.org/http://dx.doi.org/10.1111/1471-0528.12870
100. Spielberger C, Gorsuch R, Lushene R, et al. Manual for the Stait-Trait Anxiety Inventory (Form Y1–Y2). Palo Alto, CA: Consulting Psychology Press; 1983. PMID: None.
101. Goldberg D. Manual of the General Health Questionnaire. Windsor: NFER-Nelso: 1978. PMID: None.
102. Gewandter JS, Smith SM, McKeown A, et al. Reporting of primary analyses and multiplicity adjustment in recent analgesic clinical trials: ACTTION systematic review and recommendations. Pain. 2014;155(3):461-6. PMID: 24275257. http://dx.doi.org/10.1016/j.pain.2013.11.009
103. Moher D, Hopewell S, Schulz K, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340(c869). PMID: 20332511. http://dx.doi.org/10.1136/bmj.c869
104. Fleming TR. Clinical trials: discerning hype from substance. Ann Intern Med. 2010;153(6):400-6. PMID: 20855804. http://dx.doi.org/10.7326/0003-4819-153-6-201009210-00008
105. Thornton JG, Bewley S. Ovarian cancer screening: UKCTOCS trial. Lancet. 2016;387(10038):2601-2. PMID: 27353818. http://dx.doi.org/10.1016/S0140-6736(16)30846-7
106. Menon U. UK Collaborative Trial of Ovarian Cancer Screening. ISRCTN. 2017;ISRCTN22488978. PMID: None. http://dx.doi.org/10.1186/ISRCTN22488978
107. Pinsky PF, Yu K, Kramer BS, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecologic oncology. 2016. PMID: 27615399. http://dx.doi.org/10.1016/j.ygyno.2016.08.334
108. Pinsky PF, Zhu C, Skates SJ, et al. Potential effect of the risk of ovarian cancer algorithm (ROCA) on the mortality outcome of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. Int J Cancer. 2013;132(9):2127-33. PMID: 23065684. http://dx.doi.org/http://dx.doi.org/10.1002/ijc.27909

109. Lai T, Kessel B, Ahn HJ, et al. Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer. J. 2016;27(4):e41. PMID: 27102249. http://dx.doi.org/https://dx.doi.org/10.3802/jgo.2016.27.e41
110. Henderson JT, Harper CC, Gutin S, et al. Routine bimanual pelvic examinations: practices and beliefs of US obstetrician-gynecologists. Am J Obstet Gynecol. 2013;208(2):109 e1-7. PMID: 23159688. http://dx.doi.org/10.1016/j.ajog.2012.11.015
111. Guirguis-Blake J, Henderson J, Perdue L, et al. Screening for Gynecologic Conditions With Pelvic Examination: A Systematic Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality; 2016. PMID: None.
112. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011;43(5):420-32. http://dx.doi.org/http://dx.doi.org/10.1097/PAT.0b013e328348a6e7
113. Wennberg JE. Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ. 2002;325(7370):961-4. PMID: 12399352.
114. Evans EC, Matteson KA, Orejuela FJ, et al. Salpingo-oophorectomy at the Time of Benign Hysterectomy: A Systematic Review. Obstet Gynecol. 2016;128(3):476-85. PMID: 27500347. http://dx.doi.org/10.1097/AOG.0000000000001592
115. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: U.S. Preventive Services Task Force; 2015. PMID: None.
116. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer. 2008;18(3):414-20. PMID: 17645503. http://dx.doi.org/10.1111/j.1525-1438.2007.01035.x
117. van Nagell JR, Jr., Miller RW, DeSimone CP, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. Obstetrics & Gynecology. 2011;118(6):1212-21. PMID: 22105249. http://dx.doi.org/http://dx.doi.org/10.1097/AOG.0b013e318238d030
118. Miller RW, Pavlik EJ, Baldwin LA, et al. Complications from surgeries prompted by ovarian cancer screening. Gynecologic oncology. 2015;137:180. PMID: None. http://dx.doi.org/10.1016/j.ygyno.2015.01.452
119. Lowder JL, Oliphant SS, Ghetti C, et al. Prophylactic bilateral oophorectomy or removal of remaining ovary at the time of hysterectomy in the United States, 1979-2004. Am J Obstet Gynecol. 2010;202(6):538 e1-9. PMID: 20060093. http://dx.doi.org/10.1016/j.ajog.2009.11.030
120. Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies. Fertil Steril. 2014;102(1):192-8 e3. PMID: 24825424. http://dx.doi.org/10.1016/j.fertnstert.2014.03.041
121. Hanley GE, McAlpine JN, Pearce CL, et al. The performance and safety of bilateral salpingectomy for ovarian cancer prevention in the United States. Am J Obstet Gynecol. 2016. PMID: 27810554. http://dx.doi.org/10.1016/j.ajog.2016.10.035
122. Garcia C, Martin M, Tucker LY, et al. Experience With Opportunistic Salpingectomy in a Large, Community-Based Health System in the United States. Obstet Gynecol. 2016;128(2):277-83. PMID: 27399999. http://dx.doi.org/10.1097/AOG.0000000000001531

123. Russell MR, D'Amato A, Graham C, et al. Novel risk models for early detection and screening of ovarian cancer. Oncotarget. 2016. PMID: 27903971. http://dx.doi.org/10.18632/oncotarget.13648
124. Drescher CW, Hawley S, Thorpe JD, et al. Impact of screening test performance and cost on mortality reduction and cost-effectiveness of multimodal ovarian cancer screening. Cancer Prev Res (Phila). 2012;5(8):1015-24. PMID: 22750949. http://dx.doi.org/http://dx.doi.org/10.1158/1940-6207.CAPR-11-0468

Figure 1. Analytic Framework and Key Questions



Key Questions

1. Does screening for ovarian cancer in asymptomatic women using a single test or combined algorithm [such as, but not limited to, testing for serum cancer antigen (CA–125) and ultrasonography] 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?

Table 1. Characteristics of Ovarian Cancer Screening Randomized Trials

Trial, Year of publication				
Quality	Good	Good	Fair	Good
Included Key Questions	1, 2	1, 2	2	1, 2
Country	U.K.	U.S.	U.S.	U.K.
Study dates	2001-2014	1993-2010*	NR	1989-1998
Randomization allocation	1:1:2 (CG)	1:1	1:1	1:1
N randomized	202,638	78,216	592	21,955
N analyzed	202,546	68,557†	549	21,935
Key outcomes reported	KQ1: Ovarian cancer incidence and mortality KQ2: Screening false positive rates and surgical complications	KQ1: Ovarian cancer incidence and mortality KQ2: Screening false positive rates and surgical complications	KQ2: Psychological harms of screening program participation	KQ1: Ovarian cancer incidence and mortality KQ2: Screening false positive rates and surgical complications
Enrollment/ recruitment source	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.	Community volunteers from the catchment areas of 10 screening centers	Population volunteers, physician referral	Community volunteers and postal invitations to 40 primary care practices in England, Scotland, and Wales
Inclusion criteria	Post-menopausal, age 50-74	Aged 55-74	Age ≥30	Post-menopausal, age ≥45
Exclusion criteria	Self-reported history of bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, active nonovarian malignancy	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 years; pervious surgical removal of lung or entire colon; participation in other screening trial‡	High risk of ovarian cancer§; cancer diagnosis in past year; plans to become pregnant in the following 2 years	History of bilateral oophorectomy, ovarian cancer, or any active malignancy

* Additional mortality data published through 2012[107]

† 9,659 women excluded from analysis due to oophorectomy prior to trial entry (included in n randomized because they were screened for other cancers in PLCO)

‡ Exclusion based on CRC screening began in April 1995. Trial initially excluded women with of previous oophorectomy (dropped in 1996) and current tamoxifen use (dropped in 1999)

§ High risk of ovarian cancer: reported family history predicted at least a 10% probability of a germline mutation in the BRCA1or BRCA2 genes or Amsterdam criteria for hereditary nonpolyposis colorectal cancer syndrome[124]

Abbreviations: CG = control group; NR = not reported; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; QUEST = Quality of life, Education, and Screening Trial; U.K. = United Kingdom; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening; U.S. = United States.

Table 2. Baseline Characteristics of Ovarian Cancer Screening Trial Participants

Trial, Year of publication				
Quality	Good	Good	Fair	Good
Mean age, years	61	NR	NR	56
Age distribution	IQR: 56.0-66.2	55-59: 34.2% 60-64: 30.3% 65-69: 21.9% 70-74: 13.6%	30-49: 54.1%* >49: 45.9%*	45-54: 40.6%† 55-64: 48.4%† 65-74: 10.0%† >74: 1.0%†
Race (%)	White: 96.4 Black: 1.4 Asian: 0.9 Other: 0.8	White, non-Hispanic: 88.5 Black, non-Hispanic: 5.7 Hispanic: 1.5 Asian/Pacific Islander: 3.5 American Indian/Alaskan Native: 0.8	White, non-Hispanic: 95 Other: 5	White: 95 Asian: 0.5 Black: 0.6 Other: 3.9
Prior hysterectomy (%)	18.8	27.2	NR	NR
Personal history of cancer (%)	6.0	Breast cancer: 3.6	9.9*	NR
Family history of breast or ovarian cancer (%)	Maternal ovarian: 1.6 Maternal breast: 6.4	17.4	17.1	NR

* Percent in screening arms only

† Data from initial prevalence screen study, n=22,000

Abbreviations: IQR = interquartile range; NR = not reported; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; QUEST = Quality of life, Education, and Screening Trial; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 3. Ovarian Cancer Screening Trial Protocols

Trial, Year of publication	UKCTOCS, 2016[87]	PLCO, 2011[86]	U.K. Pilot, 1999[93]
Quality	Good	Good	Good
Screening intervention	Arm 1: Initial CA-125 testing with ROCA algorithm used to determine risk and followup testing and assessment through clearly defined, trial specific protocols.; followup included repeat CA-125 test (intermediate risk) or repeat CA-125 and ultrasound (elevated risk) based on ROCA Arm 2: Ultrasound (primarily transvaginal); followup ultrasound for unsatisfactory or abnormal ultrasounds	Ultrasound (mainly TVU) and CA-125§	Initial CA-125 testing; followup included ultrasound for elevated CA-125 levels
Study definition of screen positive screening	Referral to surgery for suspected ovarian cancer following positive screening and clinical assessment	Abnormal CA-125 or ultrasound	Referral to surgery for suspected ovarian cancer
Followup protocol for screen positive women	Clinical assessment and surgical investigation conducted by trial clinicians	Notification of patients and their primary care physicians; community care	Referral through family physician to a gynecologist for surgical investigation
Comparison group	No screening	Standard community care	No screening
Screening frequency	Annual	Annual	Annual
Maximum number of screening rounds	6 (original protocol) 7-11 (extended screening based on interim analysis)	CA-125: 4-6 depending on enrollment date. TVU: 4	3#
Median length of followup, years (range)	11.1 (IQR 10.0 - 11.0) (Range 0 – 13.6)	12.4 (IQR 10.9 -13)	NR (Range 0 - 8)
Abnormal test result definitions	CA-125 ROCA: Intermediate risk (risk ≥1/1818), elevated risk (risk ≥1/500)* Ultrasound: One or both ovaries with complex morphology, simple cysts greater 60 cm^3, or ascites	CA-125: ≥35 U/mL Ultrasound: 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	CA-125 ≥30 U/mL
Definition of cancer	Primary outcome: Malignant neoplasms of the ovary including epithelial and nonepithelial ovarian cancer and malignant neoplasms of the fallopian tube† and undesignated malignancies of the ovaries, fallopian tube, or peritoneum Secondary outcome: Ovarian (as defined above) and primary peritoneal cancer‡	Ovarian, primary peritoneal, and fallopian tube cancers‖¶	Invasive primary epithelial cancers of the ovary and fallopian tube
Identification of ovarian cancer cases and deaths	Administrative records (e.g., National Health Service), cancer registries, followup questionnaires, direct communication with participants, their families, and physicians, death certificates.	Annual questionnaire to participants, National Death Index, and population-based cancer registries (when possible).	National Health Service, followup questionnaires, communication with physicians and participant families, death certificates.

Table 3. Ovarian Cancer Screening Trial Protocols

Trial, Year of publication	UKCTOCS, 2016[87]	PLCO, 2011[86]	U.K. Pilot, 1999[93]
Confirmation of ovarian cancer cases and deaths	Blinded review of diagnosis and mortality by members of a designated panel (2 pathologists, 2 gynecological oncologists)	Blinded review of mortality by qualified (i.e., epidemiology, surgery, medicine, radiation oncology) member of a designated panel	Blinded pathology review of diagnosed cases

* CA-125 levels were changed in 2005 to maintain the % in each risk level (intermediate ≥1/3500, elevated≥1/1000). 84.6% of screens were classified using pre-2005 cutoffs.
† ICD-10 C56, C57
‡ ICD-10 C48.1, C48.2
§ Annual bimanual clinical examination of the ovaries discontinued in 1998 because no cases identified solely with this screening test
‖ ICD for Classification of Diseases for Oncology, Revision 2: C569, C481, C482, C570
¶ Borderline tumors were considered false positive screens
# All of the women in this trial (including the control group) had undergone a previous round of screening approximately 10 years prior

Abbreviations: 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 = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 4. Adherence to Screening in Ovarian Cancer Screening Trials

Trial, Year of publication			
Quality	Good	Good	Good
Completed at least one screen (%)	CA-125 ROCA: 98.9 ultrasound: 95.3	NR	85.5
Screening adherence (%)	CA-125 ROCA: 80.8 (% of screens attended) ultrasound: 78.0 (% of screens attended) Adherence in each round: CA-125 ROCA: 47.2-98.4 ultrasound: 35.9-94.9	ultrasound: 78-84 CA-125: 73-85	1st round: 79.7 2nd round: 79.3 3rd round: 77.4 (70.7% completed all 3 screens)
Screening contamination in control group %	4.3*	ultrasound: 2.3 - 3.2 per year CA-125: 2.7 - 4.6 per year	NR

* Self-reported ultrasound or CA-125 screening in the control arm over the entire trial period

Abbreviations: CA-125 = cancer antigen 125; NR = not reported; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; U.K. = United Kingdom; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 5. Benefits Reported in Ovarian Cancer Screening Trials: Ovarian Cancer Mortality*

Trial, Year of publication				
Quality	Good	Good	Good	Good
N analyzed per arm	IG: 50,624 CG: 101,299	IG: 50,623 CG: 101,299	IG: 34,253 CG: 34,304	IG: 10,958 CG: 10,977
Ovarian cancer incidence, n (%)	IG: 354 (0.7) CG: 645 (0.6)	IG: 324 (0.6) CG: 645 (0.6)	IG: 212 (0.6) CG: 176 (0.5)	IG: 16 (0.1) CG: 20 (0.2)
Ovarian cancer incidence rate **Between group difference**	IG: 6.4 per 10,000 p-y CG: 5.9 per 10,000 p-y p= NR	IG: 5.9 per 10,000 p-y CG: 5.9 per 10,000 p-y p=NR	IG: 5.7 per 10,000 p-y CG: 4.7 per 10,000 p-y RR 1.21 (95% CI, 0.99 to 1.48)	NR
Ovarian cancer mortality, n (%)	IG: 160 (0.32) CG: 358 (0.35)	IG: 163 (0.32) CG: 358 (0.35)	IG: 118 (0.34) CG: 100 (0.29)‡	IG: 9 (0.082) CG: 18 (0.16)
Ovarian cancer mortality rate	IG: 2.9 per 10,000 p-y CG: 3.3 per 10,000 p-y	IG: 3.0 per 10,000 p-y CG: 3.3 per 10,000 p-y	IG: 3.1 per 10,000 p-y CG: 2.6 per 10,000 p-y	NR
Ovarian cancer mortality between group difference	HR: 0.89 (95% CI, 0.74 to 1.08), p=0.23†	HR: 0.91 (0.76, 1.09), p=0.31†	RR: 1.18 (95% CI, 0.82 to 1.71) p=NR§	RR: 0.5 (95% CI, 0.22 to 1.11) p=0.083¶
Ovarian cancer survival	NR	NR	Survival difference from date of randomization p = 0.67 Survival difference from date of diagnosis (lead time bias), p = 0.18.	IG: survival 72.9 months (median) CG: 41.8 months (median) Survival difference from date of randomization, p=0.011#
Ovarian cancer treatment	NR	NR	Surgery with systemic chemotherapy IG: 171 (81%) CG: 140 (80%) p=NR, NS	NR

* Includes ovarian, fallopian, and primary peritoneal cancers
† Cox model
‡ Extended mortality data reported in results text
§ Sequentially adjusted
‖ Does not include peritoneal cancer
¶ Calculated (article reports RR calculated in in terms of increased relative risk)
# Log rank

Abbreviations: CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; NR = not reported; NS = not significant; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; P-Y = person-years; RR = relative risk; U.K. = United Kingdom; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 6. Harms Reported in Ovarian Cancer Screening Trials: Positive Testing, False Positive Testing, and Surgical Complications in Ovarian Cancer Screening*

Trial, Year of publication				
Quality	Good	Good	Good	Good
Prevalence of positive screen by round, % (n positive test/N screened)†	Round 1: 9.1 (4,555/50,078)	Round 1: 12.0 (5779/48,230)	Round 1: 5.9 (1,706/28,816) Round 2: 4.9 (1341/27541) Round 3: 4.6 (1224/2658) Round 4: 4.5 (1148/25423)	Round 1: 3.2 (284/8,732) Round 2: 1.5 (163/10936) Round 3: 3.0 (334/10925)
Cumulative prevalence of positive screen, % (n with positive test/N screened)†	Rounds 2 to 11: 44.3 (20,485/46,237)	NR	Overall screening program: 9.8 (3,358/34,253)	Overall screening program: 4.3 (468/10958)
False positive rate: Women without cancer who had a positive screening result, % (n with false positive screen/N women without cancer)	Prevalence round: 9.0 (4,513/50,031)§ Rounds 2 to 11: 44.2 (20,340/46,067)	Prevalence round: 11.9 (5,734/48,177)§ NR for subsequent rounds	Overall screening program: 9.6 (3,285/34,041)	Overall screening program: 4.2 (462/10,942)§
False positive surgery rate: Women without cancer undergoing surgery, % (n surgery/N women without cancer)	0.97 (488/50,270)	3.25 (1634/50,299)	3.17 (1,080/34,041)	0.2 (23/10,942)§
Screening test complications	0.86 per 10,000 screens‖	1.86 per 10,000 screens††	CA-125: 58.3 per 10,000 women§§ TVU: 3.3 per 10,000 women§§	NR
Women without cancer with surgical complications, % (n complication/N with false positive surgery)‡	3.07 (15/488)¶	3.49 (57/1,634)‡‡	15.09 (163/1,080)‖‖	0 (0)
Deaths from other causes	IG: 3376 (6.7%) 61.5 per 10,000 p-y# CG: 6658 (6.6%) 60.7 per 10,000 p-y# RR: 0.99, p=0.65**	IG: 3262 (6.4%) 59.4 per 10,000 p-y# CG: 6658 (6.6%) 60.7 per 10,000 p-y# RR: 0.99, p=0.65**	IG: 2924 (76.6 per 10,000 p-y) ¶¶ CG: 2914 (76.2 per 10,000 p-y) ¶¶ RR: 1.01 (95% CI, 0.96 to 1.06) p=NR	NR

* Includes ovarian, fallopian, and primary peritoneal cancers
† Patient experience of first positive screening test result leading to additional triage/followup (including repeated testing due to unsatisfactory results).
‡ Among women with false positive results/benign findings who underwent surgery
§ Does not include peritoneal cancers
‖ Includes: Bruising (13), pain (8), hematoma (3), fainting (1), cystitis/infection (1), other (4)
¶ 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)
# Excludes ovarian and primary peritoneal cancer deaths
** RR mortality ratio for no screening group vs CA-125 ROCA and ultrasound groups combined
†† Includes: Pain (20), cystitis/infection (11), discomfort (5), bruising (2), fainting (1), other (22)
‡‡ Includes: Injury to hollow viscus (4 gastrointestinal, 3 bladder, 1 ureter), hemorrhage (11), anesthetic complication/myocardial infarction (3), hernia (6), deep vein thrombosis/pulmonary embolism (3), wound breakdown (6), bowel obstruction (4), wound/supravaginal hematoma (4), infection (6), pain with readmission or further operation (3)

Table 6. Harms Reported in Ovarian Cancer Screening Trials: Positive Testing, False Positive Testing, and Surgical Complications in Ovarian Cancer Screening*

§§ Minor complications (e.g., fainting, bruising)
‖‖ 222 total complications in 163 patients. Includes: Infection (89), direct surgical harms (63), cardiovascular or pulmonary events (31), or other (39)
¶¶ Excludes deaths from ovarian, colorectal, and lung cancer

Abbreviations: CA-125 = cancer antigen 125; CG = control group; CI = confidence interval; IG = intervention group; NR = not reported; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; P-Y = person-years; RR = relative risk; TVU = transvaginal ultrasound; U.K.= United Kingdom; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 7. Harms Reported in Ovarian Cancer Screening Trials: Psychological Effects of Screening

Trial, Author, Year of publication		
Quality	Good	Fair
Population	Random sample from UKCTOCS: CA-125 ROCA: 301 ultrasound: 283 CG: 755 Event sample*: CA-125 ROCA: 12,357 ultrasound: 9,678	All screened patients participating in Quality of Life, Education, and Screening Trial (QUEST): IG: 292, CG: 150
Measures	Spielberger State/Trait Anxiety Inventory, General Health Questionnaire 12	QoL: SF-36 Mental and Physical Health scores Distress: Impact of Events Scale Cancer worry: Modified Lerman cancer worry scale
Psychological effect of screening	Random sample: no evidence of difference in state anxiety between screening and control groups	QoL, Distress, Cancer Worry: No statistically significant differences between study arms
Psychological effects of abnormal results or repeat screenings	Random sample: No evidence of change in anxiety or psychological morbidity due to repeat screenings compared with annual screen. Event sample: Compared with a single repeat screen: evidence of higher anxiety for multiple repeat scans ($p<0.010$) (small absolute effect); greater odds of psychological morbidity (GHQ-12: score $\geq$ 4) with higher level referral screening: OR 1.28 (95% CI, 1.18 to 1.39)	Women with abnormal test results (n=32) compared with women with no abnormal results more likely to report cancer worry at 2 year followup (OR 2.8; 95% CI, 1.1 to 7.2)

* All women in the screening arms recalled for repeat screening (excluding those in the random sample)

Abbreviations: CG = control group; CI = confidence interval; GHQ-12 = General Health Questionnaire 12; OR = odds ratio; QoL = quality of life; QUEST = Quality of life, Education, and Screening Trial; SF-36 = 36-Item Short Form Survey; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Table 8. Summary of Evidence

Test	# studies (k), sample size (n) Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
CA-125	k=2 n=173,858 RCT	**Ovarian cancer mortality (k=2, n=173,858).** Screening with CA-125 did not result in improved ovarian cancer mortality compared with no screening (UKCTOCS[87] HR, 0.89 [95% CI, 0.74 to 1.08], U.K. Pilot[93] RR, 0.5 [95% CI, 0.22 to 1.11])	Reasonably consistent Reasonably precise	Undetected	Good	Followup data incomplete beyond 10 years for a substantial proportion of trial participants	Moderate	Trial evidence from the U.K., 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 U.S. Study enrolled mostly white women. UKCTOCS[87] began in 2001. FDA does not support ROCA screening algorithm.
Transvaginal ultrasound	k=1 n=151,922 RCT	**Ovarian cancer mortality (k=1, n=151,922).** TVU screening did not result in improved ovarian cancer mortality compared with usual care (UKCTOCS[87] HR, 0.91 [95% CI, 0.76 to 1.09])	Consistency NA Reasonably precise	Undetected	Good	Followup data incomplete beyond 10 years for a substantial proportion of trial participants	Moderate	Trial evidence from the U.K., 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 U.S. Study enrolled few nonwhite participants.
CA-125 and transvaginal ultrasound	k=1 n=68,557 RCT	**Ovarian cancer mortality (k=1, n=68,557).** No reduction found in ovarian cancer mortality from combined TVU and CA-125 screening compared with usual care (PLCO[86] RR, 1.18 [95% CI, 0.82 to 1.71])	Consistency NA Reasonably precise	Undetected	Good	Changes to protocol, ovarian palpation dropped after first 4 trial years	Moderate	U.S. multisite trial with usual care control condition and referral to community clinicians for screen positives. Majority white, non-Hispanic study participants. Trial begun in 1993.

Table 8. Summary of Evidence

Test	# studies (k), sample size (n) Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
KQ2: Harms								
CA-125	k=3 n=242,415 RCT	**False positive rate from screening (k=2, n= 173,858).** False positive rates over multiple rounds of screening ranged from 4.2% to 44.3%. **Complications from screening (k=2, n= 220,480).** 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 (k=2, n=173,858).** False positive surgeries occurred in 0.2% to 1% of those screened with CA-125. **Complications from false positive surgery (k=2, n=173,858).** One larger trial (n=151,923) reported complications in 3.1% of false positive surgeries. One smaller trial (n=21,935) reported no surgical complications. **Psychological effects of screening (k=1, n= 13,413).** 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 arms.	Reasonably consistent or NA Reasonably precise	Undetected	Good	Psychological harms measured only for subsets of trial participants	Moderate (Low for psychological harms)	Trial evidence from the U.K., 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 U.S.

Table 8. Summary of Evidence

Test	# studies (k), sample size (n) Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
Transvaginal ultrasound	k=2 n=220,479 RCT	**False positive rate and complications from screening (k=1, n= 151,922).** False positive rate of 11.9% was reported in the initial screening round. **Complications from screening (k=2, n= 220,479).** Complications from screening with TVU ranged from 1.86 per 10,000 screens to 3.3 per 10,000 women. **False positive surgery (k=1, n=151,922).** False positive surgeries occurred in 3.2% of those screened with TVU. **Complications from false positive surgery (k=1, n= 151,922).** Complications occurred in 3.5% of false positive surgeries. **Psychological effects of screening (k=1, n=10,716).** 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 arms.	Reasonably consistent or NA Reasonably precise	Undetected	Good	Psychological harms measured only for subsets of trial participants Data on cumulative false positive rate not reported	Moderate (Low for psychological harms)	Screening conducted in specialized trial centers. Treatment for cancer (in all study arms) was through the centralized National Health Service system in U.K. and in community care settings in U.S.

Table 8. Summary of Evidence

Test	# studies (k), sample size (n) Design	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for KQ	Applicability
CA-125 and transvaginal ultrasound	k=2 n=69,106 RCT	**False positive rate and complications from screening (k=1, n=68,557).** False positive screening rate of 5.9% was reported for the first round of screening and 9.8% for the entire screening program. **Complications from screening (see complication rates for individual components).** **False positive rate for screen positive surgery (k=1, n=68,557).** False positive surgeries occurred in 3.2% of those screened. **Complications from false positive surgery (k=1, n=68,557).** Complications occurred in 15.1% of false positive surgeries. **Psychological effects of screening (k=1, n=549).** Women with abnormal test results (n=32) compared with women with no abnormal results more likely to report cancer worry at 2 year followup (OR, 2.8 [95% CI, 1.1 to 7.2]).	Consistency NA Reasonably precise (except psychological harms [imprecise])	Undetected	Fair to Good	Psychological harms measured only for subsets of trial participants	Moderate (Low for psychological harms)	U.S.-based, multisite trial. Pragmatic trial with usual care control condition and referral to community clinicians for screen positives. Majority white, non-Hispanic participants.

Abbreviations: CI = confidence interval; FDA = U.S. Food and Drug Administration; HR = hazard ratio; OR = odds ratio; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; QUEST = Quality of life, Education, and Screening Trial; RR = risk ratio; TVU = transvaginal ultrasound; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
adj# = adjacent within x number of words
ae = adverse effects
hw = subject heading word
id = identifier
kw = keyword
md = methodology
near/# = adjacent within x number of words
ti = word in title

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 (ovar* or (fallopian next tub*) or adenx*):ti,ab,kw near/4 (cancer* or neoplas* or tumo* or malignan* or carcinoma* or adenocarcinoma* or mass*):ti,ab,kw
#2 screen*:ti,ab,kw
#3 detect*:ti
#4 (sonog* or ultraso*):ti,ab,kw
#5 (tumo* next marker*):ti,ab,kw
#6 (serum next cancer next antigen*):ti,ab,kw
#7 "CA 125":ti,ab,kw
#8 96-#7
#9 #1 and #8 Publication Year from 2003 to 2016, in Trials

MEDLINE

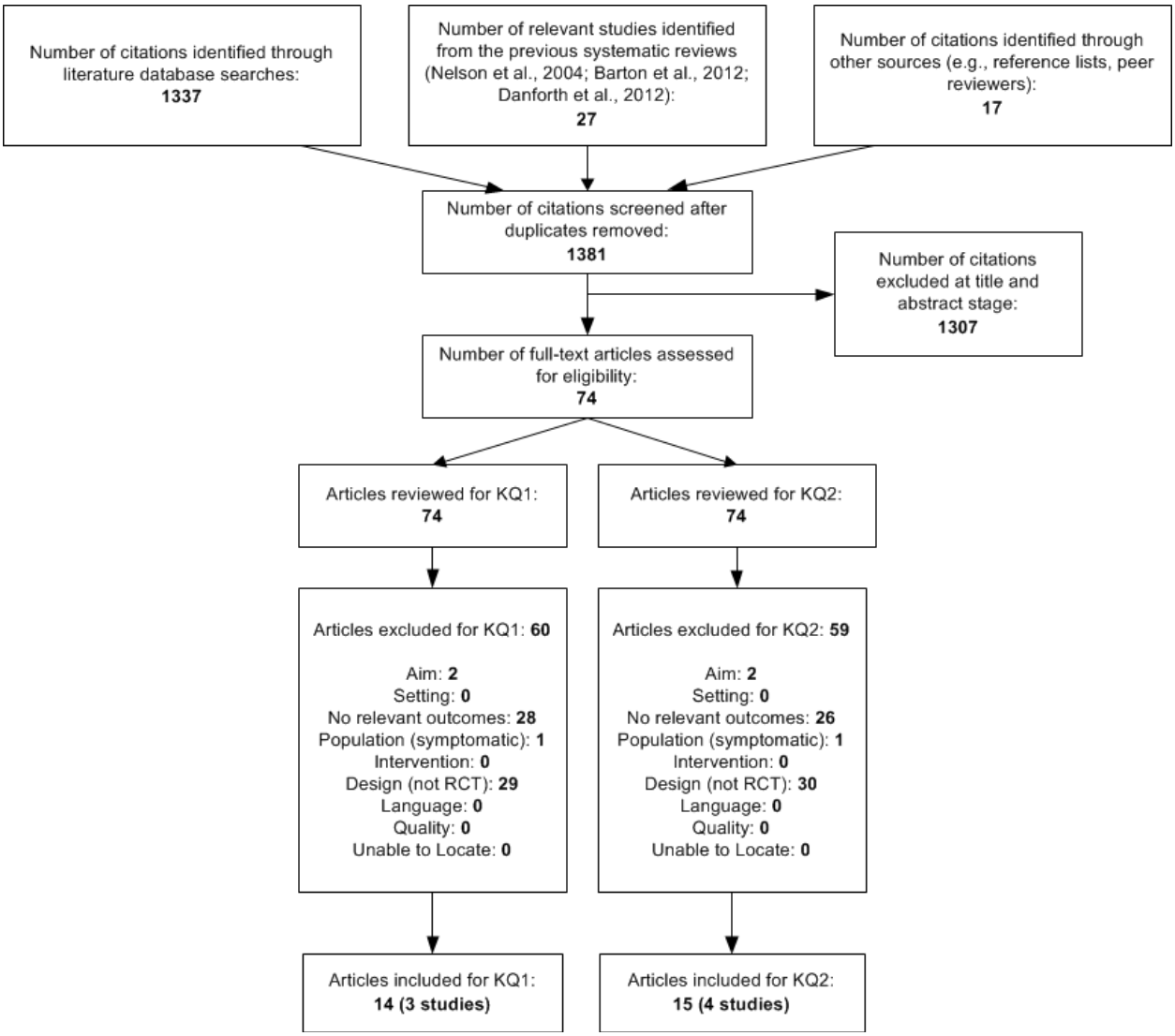
1 Ovarian Neoplasms/
2 Fallopian Tube Neoplasms/
3 ((ovar$ or fallopian tub$ or adenx$) adj4 (cancer$ or neoplas$ or tumo$ or malignan$ or carcinoma$ or adenocarcinoma$ or mass$)).ti,ab.
4 or/1-3
5 Mass screening/
6 "Early detection of cancer"/
7 (screen$ adj5 (ovar$ or fallopian tub$ or adnex$)).ti,ab.
8 detect$.ti.
9 Ultrasonography/
10 (sonog$ or ultraso$).ti,ab.
11 Tumor Markers, Biological/
12 tumo?r marker$.ti,ab.
13 serum cancer antigen$.ti,ab.
14 CA 125.ti,ab.
15 algorithm$.ti,ab.
16 ROCA.ti,ab.
17 or/5-16
18 4 and 17
19 Ovarian Neoplasms/us [Ultrasonography]
20 Fallopian Tube Neoplasms/us [Ultrasonography]
21 18 or 19 or 20

22 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
23 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
24 Random$.ti,ab.
25 control groups/ or double-blind method/ or single-blind method/
26 clinical trial$.ti,ab.
27 controlled trial$.ti,ab.
28 meta analy$.ti,ab.
29 or/22-28
30 21 and 29
31 Animals/ not (Humans/ and Animals/)
32 30 not 31
33 limit 32 to (english language and yr="2003 -Current")
34 remove duplicates from 33

PUBMED, publisher-supplied records

#14 Search (((#13) AND publisher[sb]) AND ("2003/01/01"[Date - Publication]: "3000"[Date - Publication])) AND English[Language]
#13 Search #8 AND #12
#12 Search #9 OR #10 OR #11
#11 Search (control[tiab] OR controls[tiab] OR controlled[tiab] OR controled[tiab]) AND (trial[tiab] OR trials[tiab])
#10 Search "clinical trial"[tiab] OR "clinical trials"[tiab] OR random*[tiab]
#9 Search systematic review[sb] OR metaanaly*[tiab] OR meta analysis[tiab]
#8 Search #1 AND #7
#7 Search #2 OR #3 OR #4 OR #5 OR #6
#6 Search CA 125[tiab]
#5 Search serum cancer antigen*[tiab]
#4 Search tumo* marker*[tiab]
#3 Search sonog*[tiab] or ultraso*[tiab]
#2 Search screen*[tiab] OR detect*[tiab]
#1 Search (ovar*[tiab] or fallopian tub*[tiab] or adenx*[tiab]) AND (cancer*[tiab] or neoplas*[tiab] or tumor*[tiab] OR tumour*[tiab] or malignan*[tiab] or carcinoma*[tiab] or adenocarcinoma*[tiab] or mass*[tiab])

Appendix A Figure 1. Literature Flow Diagram



Appendix A Table 1. Inclusion and Exclusion Criteria

Category		
Aim	Screening for ovarian cancer in a primary care setting (alone or as part of a clinical examination)	Screening for ovarian cancer in selected high-risk populations, such as women who are BRCA mutation carriers or patients of a specialty practice, such as oncology
Populations	Asymptomatic, average risk women, ages 45 years and older	Trials enrolling only women who are selected based on an increased risk for ovarian cancer (e.g. known predisposing genetic syndromes, strong family history)
Screening tests	Screening tests and approaches evaluated in clinical trials such as, but not limited to: testing for serum cancer antigen (CA–125), transvaginal ultrasonography, and combined screening approaches or algorithms	Screening tests not evaluated in clinical trials
Comparisons	Comparison of screening with usual care or no screening; comparison of different included screening methods or programs	
Outcomes	KQ 1: Ovarian cancer–specific mortality (including primary peritoneal and fallopian tube cancer), all-cause mortality, cancer-related morbidity, and quality of life. KQ 2: Surgery rate, rates of false-positive screening results, complications of diagnostic surgical procedures, and health and psychological effects of screening tests	
Settings	Primary care settings, including obstetrics/gynecology practices	Specialty practice settings, such as oncology

Abbreviations: USPSTF = United States Preventive Services Task Force

Appendix B. Included Studies

USPSTF quality rating criteria[115]
• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered • Intention-to-treat analysis

Appendix B. Included Studies

Below is a list of included studies and their ancillary publications (indented below main results publication):

1. Andersen MR, Drescher CW, Zheng Y, et al. Changes in cancer worry associated with participation in ovarian cancer screening. Psychooncology. 2007;16(9):814-20. PMID: 17225260. http://dx.doi.org/10.1002/pon.1151
    a. Drescher CW, Nelson J, Peacock S, et al. Compliance of average- and intermediate-risk women to semiannual ovarian cancer screening. Cancer Epidemiol Biomarkers Prev. 2004;13(4):600-6. PMID: 15066925.
2. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011;305(22):2295-303. PMID: 21642681. http://dx.doi.org/10.1001/jama.2011.766
    a. Lai T, Kessel B, Ahn HJ, et al. Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer. J. 2016;27(4):e41. PMID: 27102249. https://dx.doi.org/10.3802/jgo.2016.27.e41
    b. Buys SS, Partridge E, Greene MH, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 2005;193(5):1630-9. PMID: 16260202. http://dx.doi.org/10.1016/j.ajog.2005.05.005
    c. Croswell JM, Kramer BS, Kreimer AR, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. Ann Fam Med. 2009;7(3):212-22. PMID: 19433838. http://dx.doi.org/http://dx.doi.org/10.1370/afm.942
    d. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009;113(4):775-82. PMID: 19305319. http://dx.doi.org/http://dx.doi.org/10.1097/AOG.0b013e31819cda77
    e. Pinsky PF, Yu K, Kramer BS, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecol Oncol. 2016. PMID: 27615399. http://dx.doi.org/10.1016/j.ygyno.2016.08.334
    f. Pinsky PF, Zhu C, Skates SJ, et al. Potential effect of the risk of ovarian cancer algorithm (ROCA) on the mortality outcome of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. Int J Cancer. 2013;132(9):2127-33. PMID: 23065684. http://dx.doi.org/http://dx.doi.org/10.1002/ijc.27909
3. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2015. PMID: 26707054. http://dx.doi.org/10.1016/s0140-6736(15)01224-6
    a. Barrett J, Jenkins V, Farewell V, et al. Psychological morbidity associated with ovarian cancer screening: results from more than 23,000 women in the randomised trial of ovarian cancer screening (UKCTOCS). BJOG. 2014;121(9):1071-9. PMID: 24865441. http://dx.doi.org/http://dx.doi.org/10.1111/1471-0528.12870
    b. Jenkins V, Fallowfield L, Langridge C, et al. Psychosocial Factors Associated With Withdrawal From the United Kingdom Collaborative Trial of Ovarian Cancer Screening After 1 Episode of Repeat Screening. Int J Gynecol Cancer. 2015;25(8):1519-25. PMID: 26222482. http://dx.doi.org/http://dx.doi.org/10.1097/IGC.0000000000000507
    c. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers:

results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol. 2009;10(4):327-40. PMID: 19282241. http://dx.doi.org/10.1016/S1470-2045(09)70026-9

d. Menon U, Ryan A, Kalsi J, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015;33(18):2062-71. PMID: 25964255. 10.1200/JCO.2014.59.4945
e. Sharma A, Burnell M, Gentry-Maharaj A, et al. Quality assurance and its impact on ovarian visualization rates in the multicenter United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Ultrasound Obstet Gynecol. 2016;47(2):228-35. PMID: 26095052. http://dx.doi.org/http://dx.doi.org/10.1002/uog.14929

4. Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. Lancet. 1999;353(9160):1207-10. PMID: 10217079. http://dx.doi.org/10.1016/s0140-6736(98)10261-1
   a. Jacobs I, Davies AP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. BMJ. 1993;306(6884):1030-4. PMID: 8490497. http://dx.doi.org/10.1136/bmj.306.6884.1030

Appendix C. Excluded Studies

Reason for Exclusion*	
E1.	Study aim
E2.	Study design (not RCT)
E3a.	Setting: Not conducted in a 'very high' HDI country
E3b.	Setting: Not primary care
E4a.	Population: High-risk (genetic or family history)
E4b.	Population: Symptomatic
E5.	No relevant outcomes or incomplete outcomes
E5a.	Detection rate only
E6.	Study quality: Poor quality rating
E7.	Language: Publication not in English
E8.	Intervention is not a screening test (i.e., staging, prognostic testing)

***** Assigned at abstract and full-text phase

Abbreviations: E = exclude; HDI = human development index; KQ = key question; RCT = randomized, controlled trial

1. European randomized trial of ovarian cancer screening (protocol). London: 1995. PMID: **KQ1E5, KQ2E5.**
2. Screening CA-125 and transvaginal ultrasound does not reduce ovarian cancer mortality. J Natl Med Assoc. 2012;104(1-2):116-7. **KQ1E1, KQ2E1.**
3. Adonakis GL, Paraskevaidis E, Tsiga S, et al. A combined approach for the early detection of ovarian cancer in asymptomatic women. Eur J Obstet Gynecol Reprod Biol. 1996;65(2):221-5. **KQ1E2, KQ2E2.**
4. Akulenko LV, Gar'kavtseva RF, Zhordania KI, et al. [Current status and perspectives for genetic consultation and prophylactic medical examination of risk groups with malignant neoplasms of the female reproductive system and breast]. TSitologiia i genetika. 1992;26(1):38-42. **KQ1E2, KQ2E2.**
5. Andolf E, Svalenius E, Astedt B. Ultrasonography for early detection of ovarian carcinoma. British journal of obstetrics and gynaecology. 1986;93(12):1286-9. PMID: 3542015. **KQ1E2, KQ2E2.**
6. Belinson JL, Okin C, Casey G, et al. The familial ovarian cancer registry: progress report. Cleveland Clinic journal of medicine. 1995;62(2):129-34. PMID: 7736630. **KQ1E2, KQ2E2.**
7. Bell R, Petticrew M, Luengo S, et al. Screening for ovarian cancer: a systematic review. Health Technol Assess. 1998;2(2):i-iv, 1-84. PMID: 9561894. **KQ1E2, KQ2E2.**
8. Bourne TH, Campbell S, Reynolds K, et al. The potential role of serum CA 125 in an ultrasound-based screening program for familial ovarian cancer. Gynecologic oncology. 1994;52(3):379-85. PMID: 8157195. **KQ1E2, KQ2E2.**
9. Bourne TH, Campbell S, Reynolds KM, et al. Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. BMJ. 1993;306(6884):1025-9. PMID: 8490496. **KQ1E2, KQ2E2.**
10. Burnell M, Gentry-Maharaj A, Ryan A, et al. Impact on mortality and cancer incidence rates of using random invitation from population registers for recruitment to trials. Trials. 2011;12:61. PMID: 21362184. **KQ1E5, KQ2E5.**
11. Campbell S, Bhan V, Royston P, et al. Transabdominal ultrasound screening for early ovarian cancer. BMJ. 1989;299(6712):1363-7. PMID: 2513964. **KQ1E2, KQ2E2.**
12. Demidov VN, Krasnikova SP, Terskaia LV. [Role of echography in early detection of ovarian tumors]. Vopr Onkol. 1990;36(11):1365-8. PMID: 2281643. **KQ1E2, KQ2E2.**
13. Dorum A, Kristensen GB, Abeler VM, et al. Early detection of familial ovarian cancer. Eur J Cancer. 1996;32a(10):1645-51. **KQ1E2, KQ2E2.**
14. Drescher C, Nelson J, Peacock S, et al. Compliance of average- and intermediate-risk women to semiannual ovarian cancer screening. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology [serial on the Internet]. 2004 [cited Bridge Search 1 - CENTRAL; 13(4): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/336/CN-00502336/frame.html. **KQ1E5, KQ2E5.**
15. Gentry-Maharaj A, Sharma A, Burnell M, et al. Acceptance of transvaginal sonography by postmenopausal women participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Ultrasound Obstet Gynecol. 2013;41(1):73-9. PMID: 22791597. **KQ1E5, KQ2E5.**

16. Gohagan JK, Prorok PC, Hayes RB, et al. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Controlled clinical trials. 2000;21(6 Suppl):251s-72s. PMID: 11189683. **KQ1E5, KQ2E5.**
17. Goswamy RK, Campbell S, Whitehead MI. Screening for ovarian cancer. Clinics in obstetrics and gynaecology. 1983;10(3):621-43. PMID: 6653033. **KQ1E2, KQ2E2.**
18. Gren L, Broski K, Childs J, et al. Recruitment methods employed in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Clin. 2009;6(1):52-9. PMID: 19254935. **KQ1E5, KQ2E5.**
19. Grover S, Quinn MA, Weideman P, et al. Screening for ovarian cancer using serum CA125 and vaginal examination: report on 2550 females. Int J Gynecol Cancer. 1995;5(4):291-5. PMID: 11578492. **KQ1E2, KQ2E2.**
20. Holbert TR. Screening transvaginal ultrasonography of postmenopausal women in a private office setting. Am J Obstet Gynecol. 1994;170(6):1699-703; discussion 703-4. PMID: 8203429. **KQ1E2, KQ2E2.**
21. Jacobs I, Stabile I, Bridges J, et al. Multimodal approach to screening for ovarian cancer. Lancet. 1988;1(8580):268-71. PMID: 2893084. **KQ1E2, KQ2E2.**
22. Johnson D. The effects of an abnormal cancer screening test on health related quality of life. International Journal of Cancer Research. 2006;2:277-89. **KQ1E5, KQ2E5.**
23. Karlan BY, Raffel LJ, Crvenkovic G, et al. A multidisciplinary approach to the early detection of ovarian carcinoma: rationale, protocol design, and early results. Am J Obstet Gynecol. 1993;169(3):494-501. PMID: 8372851. **KQ1E2, KQ2E2.**
24. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer. 2008;18(3):414-20. PMID: 17645503. **KQ1E5, KQ2E5.**
25. Kurjak A, Shalan H, Kupesic S, et al. An attempt to screen asymptomatic women for ovarian and endometrial cancer with transvaginal color and pulsed Doppler sonography. J Ultrasound Med. 1994;13(4):295-301. **KQ1E2, KQ2E2.**
26. Lacey J, Greene M, Buys S, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstet Gynecol [serial on the Internet]. 2006 CENTRAL; 108(5): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/329/CN-00573329/frame.html. **KQ1E5, KQ2E5.**
27. Lacey JV, Jr., Greene MH, Buys SS, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstetrics & Gynecology. 2006;108(5):1176-84. PMID: 17077240. **KQ1E5, KQ2E5.**
28. Markman M, Petersen J, Belland A, et al. CA-125 monitoring in ovarian cancer: patient survey responses to the results of the MRC/EORTC CA-125 Surveillance Trial. Oncology. 2010;78(1):1-2. **KQ1E1, KQ2E1.**
29. Menon U, Burnell M, Sharma A, et al. Decline in use of hormone therapy among postmenopausal women in the United Kingdom. Menopause. 2007;14(3 Pt 1):462-7. PMID: 17237735. **KQ1E5, KQ2E5.**
30. Menon U, Gentry-Maharaj A, Ryan A, et al. Recruitment to multicentre trials--lessons from UKCTOCS: descriptive study.[Erratum appears in BMJ. 2008;337:a2976]. BMJ. 2008;337:a2079. PMID: 19008269. **KQ1E5, KQ2E5.**
31. Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol. 2005;23(31):7919-26. PMID: 16258091. **KQ1E5, KQ2E5.**
32. Miller RW, Pavlik EJ, Baldwin LA, et al. Complications from surgeries prompted by ovarian cancer screening. Gynecologic oncology. 2015;137:180. PMID: None. **KQ1E2, KQ2E2.**
33. Millo R, Facca MC, Alberico S. Sonographic evaluation of ovarian volume in postmenopausal women: a screening test for ovarian cancer? Clin Exp Obstet Gynecol. 1989;16(2-3):72-8. PMID: 2667810. **KQ1E2, KQ2E2.**
34. Muto MG, Cramer DW, Brown DL, et al. Screening for ovarian cancer: the preliminary experience of a familial ovarian cancer center. Gynecologic oncology. 1993;51(1):12-20. PMID: 8244166. **KQ1E2, KQ2E2.**
35. Nyante SJ, Black A, Kreimer AR, et al. Pathologic findings following false-positive screening tests for ovarian cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Gynecologic oncology. 2011;120(3):474-9. PMID: 21144559. **KQ1E5, KQ2E5.**

36. Parkes CA, Smith D, Wald NJ, et al. Feasibility study of a randomised trial of ovarian cancer screening among the general population. J Med Screen. 1994;1(4):209-14. PMID: 8790521. **KQ1E5, KQ2E5.**
37. Partridge EE, Greenlee RT, Riley TL, et al. Assessing the risk of ovarian malignancy in asymptomatic women with abnormal CA 125 and transvaginal ultrasound scans in the prostate, lung, colorectal, and ovarian screening trial. Obstetrics & Gynecology. 2013;121(1):25-31. PMID: 23262924. **KQ1E5, KQ2E5.**
38. Pinsky PF, Ford M, Gamito E, et al. Enrollment of racial and ethnic minorities in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. J Natl Med Assoc. 2008;100(3):291-8. PMID: 18390022. **KQ1E5, KQ2E5.**
39. Pinsky PF, Miller A, Kramer BS, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol. 2007;165(8):874-81. PMID: 17244633. **KQ1E5, KQ2E5.**
40. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Controlled clinical trials. 2000;21(6 Suppl):273s-309s. PMID: 11189684. **KQ1E5, KQ2E5.**
41. Reding D, Fouad M, Ragard L, et al. Prevalence, incidence and natural history of simple ovarian cysts within the context of a large cancer screening trial. Journal of Clinical Oncology. 2008;26(15_suppl):5571. PMID: 27950424. **KQ1E5, KQ2E5.**
42. Robertson DM. Screening for the early detection of ovarian cancer. Womens Health (Lond Engl). 2009;5(4):347-9. **KQ1E2, KQ2E2.**
43. Rufford BD, Jacobs IJ, Menon U. Feasibility of screening for ovarian cancer using symptoms as selection criteria. BJOG. 2007;114(1):59-64. PMID: 17233861. **KQ1E4b, KQ2E4b.**
44. Sato S, Hasuo Y, Ohta S, et al. [Mass-screening for ovarian cancer by means of transvaginal ultrasonography]. Nihon Sanka Fujinka Gakkai zasshi. 1992;44(6):683-8. PMID: 1506730. **KQ1E2, KQ2E2.**
45. Sato S, Yokoyama Y, Sakamoto T, et al. Usefulness of mass screening for ovarian carcinoma using transvaginal ultrasonography. Cancer. 2000;89(3):582-8. PMID: 10931457. **KQ1E2, KQ2E2.**
46. Schincaglia P, Brondelli L, Cicognani A, et al. A feasibility study of ovarian cancer screening: does fine-needle aspiration improve ultrasound specificity? Tumori. 1994;80(3):181-7. PMID: 8053074. **KQ1E2, KQ2E2.**
47. Schwartz PE, Chambers JT, Taylor KJ. Early detection and screening for ovarian cancer. Journal of cellular biochemistry Supplement. 1995;23:233-7. PMID: 8747402. **KQ1E2, KQ2E2.**
48. Sharma A, Apostolidou S, Burnell M, et al. Risk of epithelial ovarian cancer in asymptomatic women with ultrasound-detected ovarian masses: a prospective cohort study within the UK collaborative trial of ovarian cancer screening (UKCTOCS). Ultrasound Obstet Gynecol. 2012;40(3):338-44. PMID: 22911637. **KQ1E5, KQ2E5.**
49. Sharma A, Burnell M, Gentry-Maharaj A, et al. Factors affecting visualization of postmenopausal ovaries: descriptive study from the multicenter United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Ultrasound Obstet Gynecol. 2013;42(4):472-7. PMID: 23456790. **KQ1E5, KQ2E5.**
50. Sharma A, Gentry-Maharaj A, Burnell M, et al. Assessing the malignant potential of ovarian inclusion cysts in postmenopausal women within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2012;119(2):207-19. PMID: 21762355. **KQ1E5, KQ2E5.**
51. Tabor A, Jensen FR, Bock JE, et al. Feasibility study of a randomised trial of ovarian cancer screening. J Med Screen. 1994;1(4):215-9. PMID: 8790522. **KQ1E5, KQ2E5.**
52. Taylor KL, Shelby R, Gelmann E, et al. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst. 2004;96(14):1083-94. PMID: 15265970. **KQ1E5, KQ2E5.**
53. van Nagell JR, Jr., DePriest PD, Reedy MB, et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. Gynecologic oncology. 2000;77(3):350-6. PMID: 10831341. **KQ1E2, KQ2E2.**
54. van Nagell JR, Jr., Gallion HH, Pavlik EJ, et al. Ovarian cancer screening. Cancer. 1995;76(10 Suppl):2086-91. PMID: 8635005. **KQ1E2, KQ2E2.**
55. Vuento MH, Pirhonen JP, Makinen JI, et al. Evaluation of ovarian findings in asymptomatic postmenopausal women with color Doppler ultrasound. Cancer. 1995;76(7):1214-8. **KQ1E2, KQ2E2.**

56. Vuento MH, Stenman UH, Pirhonen JP, et al. Significance of a single CA 125 assay combined with ultrasound in the early detection of ovarian and endometrial cancer. Gynecologic oncology. 1997;64(1):141-6. PMID: 8995563. **KQ1E2, KQ2E2.**

57. Weiner Z, Beck D, Shteiner M, et al. Screening for ovarian cancer in women with breast cancer with transvaginal sonography and color flow imaging. J Ultrasound Med. 1993;12(7):387-93. PMID: 8355333. **KQ1E2, KQ2E2.**

Appendix D. Benefits Reported in Ovarian Cancer Screening Trials: Ovarian Cancer Mortality in Analyses Excluding Peritoneal Cancer*

Trial, Year of publication				
Quality	Good	Good	Good	Good
N analyzed per arm	IG: 50,624 CG: 101,299	IG: 50,623 CG: 101,299	IG: 34,253 CG: 34,304	IG: 10,958 CG: 10,977
Ovarian cancer incidence, n (%)	IG: 338 (0.7) CG: 630 (0.6)	IG: 314 (0.6) CG: 630 (0.6)	IG: 183 (0.5) CG: 158 (0.5)	IG: 16 (0.1) CG: 20 (0.2)
Ovarian cancer incidence rate **Between group difference**	IG: 6.2 per 10,000 p-y CG: 5.7 per 10,000 p-y p=NR	IG: 5.7 per 10,000 p-y CG: 5.7 per 10,000 p-y p=NR	IG: 4.9 per 10,000 p-y CG: 4.7 per 10,000 p-y p=NR	NR
Ovarian cancer mortality, n (%)	IG: 148 (0.29) CG: 347 (0.34)	IG: 163 (0.30) CG: 347 (0.34)	NR	IG: 9 (0.082) CG: 18 (0.16)
Ovarian cancer mortality rate	IG: 2.7 per 10,000 p-y CG: 3.2 per 10,000 p-y	IG: 2.8 per 10,000 p-y CG: 3.2 per 10,000 p-y	NR	NR
Ovarian cancer mortality between group difference	HR: 0.85 (95% CI, 0.70 to 1.03), p=0.10†	HR: 0.89 (0.73, 1.07), p=0.21†	NR	RR: 0.5 (95% CI, 0.22 to 1.11) p=0.083‡

* Includes ovarian and fallopian cancers
† Cox proportional hazards model
‡ Calculated (article reports RR calculated in in terms of increased relative risk)

Abbreviations: CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; NR = not reported; NS = not significant; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; P-Y = person-years; ROCA = Risk of Ovarian Cancer Algorithm; RR = relative risk; U.K. = United Kingdom; UKCTOCS: U.K. Collaborative Trial of Ovarian Cancer Screening