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Review

Risks and benefits of screening asymptomatic women for ovarian cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Screening asymptomatic women for ovarian cancer does not lead to earlier diagnosis or reduced mortality.
- Screening causes harm through unnecessary surgery, and worry from false-positive testing.
- Transvaginal ultrasound leads to the highest rate of unnecessary surgery from screening.

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ABSTRACT

Objective. We performed a systematic review and meta-analysis to quantify risks and benefits of screening asymptomatic women for ovarian cancer.

Methods. We searched MEDLINE, EMBASE, CINAHL, and Cochrane CENTRAL, without language restrictions, from January 1, 1979 to February 5, 2012. Eligible studies randomly assigned asymptomatic women to screening or usual care. Two reviewers independently screened studies for eligibility, extracted data using a standardized, piloted extraction form, and assessed bias and strength of inference for each outcome using the GRADE framework. Chance-corrected agreement was calculated at each step, and disagreements were resolved through consensus.

Results. Ten randomized trials proved eligible. Screening did not reduce all-cause mortality (relative risk (RR) = 1.0, 95% confidence interval (CI) 0.96–1.06), ovarian cancer specific mortality (RR = 1.08, 95% CI 0.84–1.38), or risk of diagnosis at an advanced stage (RR of diagnosis at FIGO stages III–IV = 0.86, 95% CI 0.68–1.11). Transvaginal ultrasound resulted in a mean of 38 surgeries per ovarian cancer detected (95% CI 15.7–178.1) while screening with CA-125 led to 4 surgeries per ovarian cancer detected (95% CI 2.7–4.5). Surgery was associated with severe complications in 6% of women (95% CI 1%–11%). Quality of life was not affected by screening; however, women with false-positive results had increased cancer-specific distress compared to those with normal results (odds ratio (OR) = 2.22, 95% CI 1.23–3.99).

Conclusions. Screening asymptomatic women for ovarian cancer does not reduce mortality or diagnosis at an advanced stage and is associated with unnecessary surgery.

Contents

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Introduction

Ovarian cancer is the most deadly gynecologic malignancy, with a 5-year relative survival of 26.9% when diagnosed in FIGO stages III–IV [1]. The goal of ovarian cancer screening is to diagnose malignant disease at an early stage, prior to spread within the peritoneal cavity. A stage-shift leading to diagnosis in stage I or II, rather than stage III or IV, could lead to decreased mortality through early curative therapy [2]. Even so, a shift to earlier stage of diagnosis would not necessarily result in a reduction in mortality if screening primarily identifies the less aggressive histological subtypes of ovarian cancer [3]. A reduction in mortality should be the primary goal of any cancer screening program.

Several methods of screening for ovarian cancer have been investigated, including transvaginal sonography (TVS) and serum CA-125. These tests, however, are non-specific (they may be abnormal with benign processes or non-gynecologic malignancy), and are not perfectly sensitive (they may be normal in cases of early ovarian cancer) [4]. Definitive diagnosis of ovarian cancer requires surgical removal of the ovaries with pathological sectioning. Since most abnormal screening tests occur in women without ovarian cancer (false positives), screening may result in harm through unnecessary follow-up testing and surgery [5].

In spite of recommendations by clinical practice guidelines against screening women at average population risk of ovarian cancer [6–9] including a 2012 update from the US Preventive Services Task Force [10], screening for ovarian cancer remains common. A national representative survey of US primary care physicians published in 2012 found one in three believed ovarian cancer screening was effective and up to 24% (95% CI 20.5%–28.0%) routinely offered screening to asymptomatic women. Screening often occurred in response to patient request (RR = 1.54; 95% CI 1.39–1.72), potentially leading to more than 1 million screens per year in the United States alone [11]. The Prostate, Lung, Colorectal and Ovarian Screening (PLCO) trial found that 9.4% of the 78,216 female participants had been screened for ovarian cancer in the three years prior to trial enrollment [5]. Primary care providers may screen despite a lack of evidence because of patient request, defensive medicine, or to relieve patient anxiety [12]. Physicians may agree to a patient's request for screening, assuming there is limited benefit but also little potential for harm. Quantification of harms related to ovarian cancer screening is therefore important information for patients and care providers.

Since the previous systematic review, which did not statistically combine outcome data or include mortality as an outcome [4], investigators have published three large randomized controlled trials (RCTs) of screening for ovarian cancer. The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) followed 82,487 women in Japan for 9.2 years [13], the PLCO trial followed 78,216 US women for 12.4 years [5,14,15], and the prevalence screening round of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) followed 202,638 women in the UK for 3–7 years [16].

We conducted a systematic review and meta-analysis of RCTs to determine the risks and benefits of ovarian cancer screening in asymptomatic women, with a focus on mortality and unnecessary surgery and its consequences.

Methods

Data sources and searches

We identified relevant RCTs, in any language, by a systematic search of MEDLINE (including in-process and non-indexed citations), CINAHL, EMBASE, and CENTRAL, from January 1, 1979 to February 5, 2012. An experienced academic librarian collaborated in the development of the search strategy of each database. The search was limited to publications from 1979 or later, four years prior to the earliest study identified by previous systematic reviews [2,4]. Two reviewers (CJR and JJR) scanned the reference lists of relevant systematic reviews and all eligible RCTs to identify additional studies. We also contacted experts in the field requesting information about unpublished or ongoing trials.

Study selection

Eligible studies included RCTs allocating asymptomatic women to either screening for ovarian cancer or no intervention, usual care, or education regarding the signs and symptoms of ovarian cancer. All forms of screening were eligible, as were trials including women at high or low risk of ovarian cancer.

Two reviewers (CJR and JJR) assessed all titles and abstracts of identified citations independently. The same reviewers independently applied eligibility criteria to the full text of each potentially eligible trial using a standardized, pilot-tested screening form. Disagreement was resolved by consensus at each stage.

Data extraction and quality assessment

Reviewers (CJR and JJR) used a standardized, piloted electronic form and detailed instruction manual to extract data independently from all eligible studies. Authors were contacted for missing data. Data extracted included demographic information, screening intervention, control arm details, and all reported patient-important outcomes. Outcomes were extracted using an intention-to-treat approach. Reviewers (CJR and JJR) independently assessed risk of bias for each eligible RCT using the Cochrane Risk of Bias Tool [17]. Disagreements were resolved by consensus.

Reviewers independently evaluated the confidence in effect estimates using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system for each outcome and achieved consensus through discussion [18]. Evidence from RCTs warrants a high degree of confidence, but may be rated down because of: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, and 5) reporting bias [19]. A rating of high quality evidence indicates