

EDITORIAL

Screening for Ovarian Cancer in Asymptomatic Women

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Developing an effective strategy for early detection of ovarian cancer remains one of the most significant unmet needs in the diagnosis and treatment of the disease. Approximately



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22 000 cases of ovarian cancer are diagnosed each year among women in the United States.¹ Similar to women with lung and pancreatic cancers, women with ovarian cancer are typically diagnosed in late stages, resulting in poor outcomes. For the 20% of patients with ovarian cancer diagnosed with stage I disease, 5-year survival rates are greater than 90%, whereas for the majority of women diagnosed with stage III or IV ovarian cancer, 5-year survival rates are approximately 17% to 39%.²

In this issue of *JAMA*, the US Preventive Services Task Force (USPSTF) provides an update to and reiterates its 2012 recommendation on screening for ovarian cancer and currently “recommends against screening for ovarian cancer in asymptomatic women. (D recommendation) This recommendation applies to asymptomatic women who are not known to have a high-risk hereditary cancer syndrome.”³ With a D recommendation, based on a rigorous evaluation of the evidence of benefits and harms of ovarian cancer screening, there is no ambiguity: no current strategy for the early detection of ovarian cancer is recommended for widespread population use in women at average risk.⁴ Over the last 3 decades there has been a strong push from both the research and clinical communities and the ovarian cancer advocacy community to identify new biomarkers and to develop an effective strategy to identify ovarian cancer at its earliest stages. With such a clear unmet need and research commitment, it is important to ask the following questions: Why has it not been possible to delineate an effective screening strategy for ovarian cancer? Is an effective strategy close at hand?

To implement a population-wide ovarian cancer screening strategy, or any cancer screening strategy, there must be evidence that the test is both sensitive enough to detect the cancer early and specific enough not to cause harm to healthy people. The gold standard is a randomized trial that demonstrates a decrease in ovarian cancer mortality among healthy women who are screened vs those not screened. Only 2 such studies large enough to evaluate mortality as the primary outcome have been conducted: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States⁵ and the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).⁶ The general rarity of ovarian cancer, with an incidence of 1 in 2500 in postmenopausal women,⁷ means that extremely

large numbers of women would be required for a clinical trial to have sufficient power to detect mortality differences related to screening.

The PLCO study enrolled almost 70 000 women and randomized them to receive usual care or to undergo annual screening (with blood testing for the cancer antigen 125 [CA-125] biomarker and transvaginal ultrasound [TVUS] for the first 4 rounds of screening, then 2 rounds of annual CA-125 testing only). After a median follow-up of approximately 12 years, there was no significant difference in ovarian cancer mortality. The findings were published in 2011, and the negative results were reflected in the 2012 USPSTF recommendation against ovarian cancer screening.

The UKCTOCS study was published in 2016 and the results are worth revisiting, because the size, scope, and results of the study provide insight into the challenges and potential of developing an effective ovarian cancer screening strategy. The UKCTOCS study included more than 200 000 women; half received routine care, one-fourth underwent annual TVUS, and one-fourth had an annual CA-125 blood test. This test was interpreted using the risk of ovarian cancer algorithm (ROCA), which examined change in CA-125 values over time, as opposed to a single CA-125 value. In the ROCA group, if the algorithm detected a rapid increase in CA-125 value compared with the value in the prior year, the woman underwent TVUS. If TVUS identified an abnormal finding in the ovary, surgery might be performed. This method has the advantage of identifying a baseline CA-125 range for each woman, instead of using a static, single-value cutoff as was used in the PLCO study.

The UKCTOCS study found that after a median of 11 years of follow-up, women in the ROCA group had about 15% fewer deaths than those in the no screening group (148 vs 347, respectively; $P = .10$). However, this decrease was not statistically significant. There was a significant shift toward detecting earlier stage/low-volume ovarian cancers in the ROCA group as compared with the control group (40% vs 26%). A prespecified subset analysis of incident cases demonstrated a 20% decrease in mortality ($P = .02$), although there were broad confidence limits around this estimate and additional follow-up will be required. Harm was, however, associated with screening. The study reported 14 instances of false-positive surgery per 10 000 screens in the ROCA group and 50 instances of false-positive surgery per 10 000 screens in the ultrasound group. In the ROCA group, no more than 2 surgical procedures were required to detect 1 case of ovarian cancer, whereas in the ultrasound group, 10 surgical procedures were required to detect 1 case of ovarian cancer. Similar specificity was obtained in the United States in a single-group

study using the same ROCA.⁸ Although the UKCTOCS study includes important information, the findings do not conclusively demonstrate the benefit of screening as conducted in the study. Specifically, the ROCA screening group demonstrated a stage shift to earlier-stage cancers and acceptable risks but did not yet demonstrate a convincing mortality benefit. The USPSTF therefore did not change its recommendation in 2018 against ovarian cancer screening for women at average risk.

Although the reduction in mortality in the ROCA group in the UKCTOCS trial did not reach statistical significance, the authors pointed out that there appeared to be a delay in observing the benefit of screening on mortality.⁶ This type of delay has been seen in other screening studies, and with women with ovarian cancer living longer with disease, this type of delay in benefit is not inconceivable. The authors used a post hoc model to project a possible 8% mortality benefit in years 0 to 7 and a 23% benefit in years 7 to 14.⁶ With an estimated need for an additional 3 years of data, the authors plan to evaluate whether there is longer-term mortality benefit in the ROCA screening group. A cost-effectiveness study from a US group used the UKCTOCS data to evaluate the cost of ROCA screening in the United States and suggested that if the long-term mortality benefit from ROCA screening does improve, and if the cost of the strategy is similar to that in the United Kingdom, general population screening with ROCA may be cost-effective.⁹ However, these estimates remain speculative and can only be confirmed after longer-term mortality data from the UKCTOCS become available.

Important lessons learned over the last 2 decades should help to develop improved strategies for early detection of ovarian cancer. First, it seems likely that effective, early detection of ovarian cancer will involve a 2-stage strategy that includes a first-stage, inexpensive test (for example,

a blood test) followed by an imaging test in a much smaller group of women with abnormal findings on first-stage testing. Although TVUS is currently used as the second-stage test, novel imaging technologies that detect much smaller volumes of abnormal cells might ultimately prove to make ovarian cancer screening more effective. Second, samples used for discovery of new biomarkers must be “prediagnostic,” ie, samples from women who ultimately developed ovarian cancer but were clinically without evidence of disease when the sample was taken. Continued new technology for biomarker discovery, including sophisticated proteomics or cell-free DNA techniques, will only be useful if appropriate samples are used. Autoantibodies have detected disease 8 months prior to CA-125 testing.¹⁰ Third, validation of candidate biomarkers is essential, and the huge biorepositories from the PLCO and UKCTOCS studies could serve to help with validation of new candidate biomarkers.

While efforts continue to identify effective strategies for early detection, to truly reduce the morbidity and mortality of ovarian cancer, a complementary prevention strategy also will be needed. It appears that many high-grade serous ovarian cancers, which are the most common type of ovarian cancer and certainly the subtype with the highest mortality burden, may not originate from the ovarian surface epithelium, as was previously believed, but rather from the fimbrial epithelium of the fallopian tube.¹¹ Early and microscopic cancers in prophylactic specimens from women with *BRCA1* or *BRCA2* genetic mutations are fallopian tube cancers, and surgical removal of the fallopian tubes and ovaries are the foundation of prevention in these high risk women.¹² Broadening the strategy to include accurate risk models and genetic testing, novel prevention options, and effective early detection may help reduce the incidence and high mortality associated with ovarian cancer.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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