OVARIAN CANCER

Recent studies shed light on early detection of ovarian cancer—but it's not a green light for routine screening. Until promising avenues of research lead further, refer women who have an adnexal mass, an elevated CA-125 level, and troubling ultrasonographic findings to a specialist—early.

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IN THIS ARTICLE

Because ovarian cancer is usually diagnosed at an advanced stage—when prognosis is much worse than earlier in its course—a great deal of effort has been directed toward developing strategies to detect it early. These strategies include screening by a woman's primary gynecologist with **1)** a test of the serum CA-125 level and **2)** transvaginal ultrasonography (TVU).

But how useful are the results of those screening tests? How should they be interpreted?

The answers aren't clear.

Recent studies have yielded new information about ovarian cancer screening and detection. We discuss them in this Update:

- Screening with serial testing of the CA-125 level and TVU still is not recommended by the US Preventive Services Task Force or by ACOG
- Initial preliminary data from a prevalence screen of more than 50,000 subjects in the United Kingdom are encouraging, and show that new screening strategies may be feasible
- Using a patient's report of her symptoms to trigger medical evaluation for ovarian cancer is not an effective screening tool
- Women who have an adnexal mass and a serum CA-125 level >35 U/mL and abnormal sonographic findings have an increased likelihood of ovarian cancer. They should be referred directly to a specialist.

The effect of screening on ovarian cancer mortality remains unknown

Partridge E, Greenlee RT, Xu J-L, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009;113(4):775–782.

The potential benefit of an effective screening program for ovarian cancer is great; the disease is the most lethal of all common gynecologic malignancies and carries significant individual and societal costs.[1] Furthermore, diagnosis at an early stage is associated with improved survival.

To date, however, studies have not shed light on whether screening with CA-125 testing or TVU has an impact on morbidity or mortality from ovarian cancer. In a large,

multicenter trial of more than 30,000 women, Partridge and colleagues attempted to answer this question.

Investigators sought to determine whether this cohort of healthy women, ranging in age from 55 to 74 years, experienced a reduction in mortality from ovarian cancer when subjects were screened annually with a combination of CA-125 testing and TVU. The study was part of a larger trial (the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial[2]).

Subjects were randomized 1:1 to **1)** the screening arm or **2)** their customary gynecologic care without screening. The regimen in the screening arm comprised:

- annual measurement of the CA-125 in Years 1 through 6
- annual TVU in Years 1 through 4
- evaluation and follow-up of positive screening tests at the discretion of each subject's treating physician.

Distribution of staging was unaffected. Overall, the positive predictive value of the screening regimen was relatively constant—and quite low—across the screening years (1.1% in Year 1 [95% confidence interval (CI), 0.6–1.6]; 1.0% in Year 2 [95% CI, 0.4–1.5]; 1.1% in Year 3 [95% CI, 0.5–1.7]; and 1.3% in Year 4 [95% CI, 0.6–2.0]).

Of 3,388 women who had at least one positive result on either screening test, 1,170 (34.5%) underwent biopsy at some point. Of those, 60 (5.1%) had invasive cancer—yielding a surgery-to-detected-cancer ratio of 19.5:1.

Approximately 70% of cancers detected by screening were a Stage-III or -IV tumor. As such, **the screening effort did not change the expected distribution of staging from what would be expected in an unscreened population**.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Do *not* yet screen your general patient population for ovarian cancer with combined annual CA-125 testing and transvaginal ultrasonography. Determination of whether screening with this strategy will reduce mortality from ovarian cancer must await the final results of the larger PLCO trial.

FAST TRACK

Screening for ovarian cancer in the general population using annual CA-125 testing and TVU is not yet recommended

Is it feasible to screen for ovarian cancer on a large scale?

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):327–340.

The low prevalence of ovarian cancer presents a significant challenge to anyone hoping to devise a useful screening program: A screening test designed to detect a low-prevalence disease **must have exceptionally high sensitivity and specificity** to achieve a clinically useful positive predictive value—especially when the intervention is relatively risky (surgical removal of the ovaries) and has known harmful health implications.

With that requirement in mind, researchers have refined ovarian cancer screening methods. One of these refinements is a risk-of-ovarian-cancer algorithm by which clinicians would be able to interpret serial CA-125 results.[3,4]

Interim results from a prevalence screen. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) evaluated these new screening methods in a multicenter, randomized, controlled trial in an effort that assessed not only mortality but also

cost, acceptance by patients, and the physical and psychosocial morbidities associated with screening. At this point, investigators are reporting the results of a prevalence screen.

The team evaluated more than 200,000 low-risk women who were randomized to either **1)** no screening, **2)** multimodal screening (MMS), or **3)** annual TVU screening, in, respectively, a 2:1:1 ratio. Multimodal screening comprised:

- annual CA-125 testing (interpreted using a risk-of-ovarian-cancer algorithm) and
- TVU as a second-line test.

Follow-up algorithms for women in both groups were determined a priori, based on a risk score ("normal," "intermediate," and "high") from initial screening results. An initial, basic level-1 sonogram was performed on all women; a subsequent, more focused level-2 sonogram was performed only if indicated.

Among women assigned to screening, the following was noted:

- fewer women in the MMS group (0.3%) required clinical evaluation than in the TVU group (3.9%)
- fewer women in the MMS group (0.2%) required surgery than in the TVU group (1.8%)
- a similar number of cancers was detected in the two groups (MMS, 42; TVU, 45)
- more borderline tumors were detected in the TVU group than in the MMS group.

MMS had higher specificity and positive predictive value than TVU (respectively: 99.8% and 98.2%; 43.3% and 5.35%). Almost 50% of cancers detected on the initial screen were Stage I or II.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Again, do *not* screen for ovarian cancer with combined annual CA-125 testing and TVU. This study suggests, however, that large-scale screening strategies are feasible, and that they may provide useful guidance. We await the results of the researchers' ongoing screening trial to determine what effects such screening might have on mortality from ovarian cancer.

FAST TRACK

Multimodal screening for ovarian cancer has higher specificity and positive predictive value than transvaginal ultrasonography alone

Symptoms are not predictive of the risk of ovarian cancer

Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst. 2010;102(4):222–229.

Evaluation of symptoms has been suggested as a way of identifying women who may be at risk of ovarian cancer. In a 2007 consensus statement on the topic, contributors note that certain symptoms—bloating, pelvic or abdominal pain, difficulty eating, early satiety—are more common in women who have ovarian cancer than they are in the general population.[5] They recommend that women who have these symptoms consult their physician for prompt evaluation.

But concerns have been raised about the true utility of these symptoms as a tool for detecting ovarian cancer at an earlier stage and, therefore, improving survival.

Linking symptom onset to time of diagnosis. Using a population-based registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the investigators conducted a large, population-based study to examine the occurrence and timing of symptoms in **1)** women who have ovarian cancer and **2)** controls. They identified women in a 13-county area of western Washington State, ranging from 35 to 74 years old, who were given a diagnosis of epithelial ovarian cancer or had a borderline epithelial ovarian tumor over a 3-year period.

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Of 1,058 eligible women who had ovarian cancer, the team interviewed 812. An additional 1,313 controls (providing a 69% response rate) were interviewed.

Results showed that most case patients who had symptoms often associated with ovarian cancer experienced those symptoms only within 5 months before their initial diagnosis. Symptoms were also less likely to occur in early-stage ovarian cancer than in late-stage disease.

The positive predictive value for the symptom index was extremely low (<0.5% in early-stage disease and 0.6%–1.1% in late-stage disease).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Proceed cautiously with use of any symptom index to trigger referral to a subspecialist, because it will detect ovarian cancer in only 1 of every 100 women in the general population whose presentation includes such symptoms. Data suggest that it will have limited utility for detecting early-stage cancer. Symptoms should not be completely ignored, however, because they do manifest more often in women who have ovarian cancer than in the general population.

Ultrasonography in combination with serum CA-125 can facilitate early referral to a subspecialist

FAST TRACK

86.8% of women who had both an adnexal mass and a serum CA-125 level of 60–120 U/mL were found to have ovarian cancer

McDonald JM, Doran S, DeSimone CP, et al. Predicting risk of malignancy in adnexal masses. Obstet Gynecol. 2010;115(4):687–694.

The finding of an adnexal mass is a common clinical scenario in gynecology. Any number of benign causes may be responsible, but it is important to identify which of those masses present a high likelihood of malignancy because complete surgical resection, along with adjuvant therapy administered in a timely manner, will maximize survival.

For that reason, an individualized risk profile in patients who have an adnexal mass confirmed by ultrasonography (US) would assist clinicians in making early referral to a cancer specialty care center.

Researchers evaluated 399 women who had been referred because of an adnexal mass on pelvic examination. Their objective was to estimate the accuracy of the following combination in predicting the risk of malignancy:

- patient demographics
- tumor morphology on US
- the serum CA-125 level.

The serum CA-125 level correlated directly with risk of malignancy in women who had an adnexal mass: Only 7.7% of women whose serum CA-125 level was within the normal range had ovarian cancer, compared with 34.2% women whose CA-125 level was 35–59 U/mL, and 86.8% whose level was 60–120 U/mL ($P < .001$). Multivariate analysis revealed that the most accurate significant predictor of a high risk of malignancy in patients who have an adnexal mass with complex or solid morphology is a serum CA-125 level >35 U/mL. This cutoff yielded a sensitivity of 77.3% for early stage ovarian cancer and 98.6% for advanced stage disease.

In summary

To repeat: As we await results of the UKCTOCS and the PLCO trial, **do *not* screen patients routinely for ovarian cancer.** Women who have an adnexal mass, an elevated CA-125 level, and troubling US findings should be referred—early—to a specialist.

References

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Refer women who have a complex or solid adnexal mass and a CA-125 level >35 U/mL to a specialist. Early referral is important: Studies have shown a survival advantage as high as 24% among patients who have early-stage ovarian cancer and are treated by a gynecologic oncologist.[6, 7]

The only benign histologic finding consistently associated with an elevated serum CA-125 level is ovarian endometriosis. In patients who have a history of endometriosis or other symptoms consistent with endometriosis, and an elevated CA-125 level, ovarian cancer is much less likely.

Also be aware that all 54 patients in this study who had ascites on US had invasive epithelial ovarian cancer, giving that finding a positive predictive value of 100%.