

14. Screening for Ovarian Cancer

RECOMMENDATION

Routine screening for ovarian cancer by ultrasound, the measurement of serum tumor markers, or pelvic examination is not recommended. There is insufficient evidence to recommend for or against the screening of asymptomatic women at increased risk of developing ovarian cancer.

Burden of Suffering

Ovarian cancer is the fifth leading cause of cancer deaths among U.S. women and has the highest mortality of any of the gynecologic cancers.¹ It accounted for an estimated 26,600 new cases and 14,500 deaths in 1995.¹ The lifetime risk of dying from ovarian cancer is 1.1%.^{1a} The overall 5-year survival rate is at least 75% if the cancer is confined to the ovaries and decreases to 17% in women diagnosed with distant metastases.^{2,3} Symptoms usually do not become apparent until the tumor compresses or invades adjacent structures, ascites develops, or metastases become clinically evident.⁴ As a result, two thirds of women with ovarian cancer have advanced (Stage II or IV) disease at the time of diagnosis.^{2,5,6} Carcinoma of the ovary is most common in women over age 60.⁷ Other important risk factors include low parity and a family history of ovarian cancer.⁸⁻¹⁰ Less than 0.1% of women are affected by hereditary ovarian cancer syndrome, but these women may face a 40% lifetime risk of developing ovarian cancer.¹¹

Accuracy of Screening Tests

Potential screening tests for ovarian cancer include the bimanual pelvic examination, the Papanicolaou (Pap) smear, tumor markers, and ultrasound imaging. The pelvic examination, which can detect a variety of gynecologic disorders, is of unknown sensitivity in detecting ovarian cancer. Although pelvic examinations can occasionally detect ovarian cancer,^{12,13} small, early-stage ovarian tumors are often not detected by palpation,^{14,15} due to the deep anatomic location of the ovary. Thus, ovarian cancers detected by pelvic examination are generally advanced^{7,16-18} and associated with poor survival.¹⁶ The pelvic examination may also produce false positives when benign adnexal masses (e.g., functional cysts) are found.^{16,19} The Pap smear may occasionally reveal malignant ovarian cells,²⁰ but it is not con-

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considered a valuable indicator for ovarian carcinoma.^{16-18, 21} Studies indicate that CA-125 is elevated in women with ovarian cancer of only 10-30%.¹⁶ Other tumor markers include carcinoembryonic antigen, ovarian cancer-associated sialic acid, NB/70K, TAG, and CA-158. CA-125 is elevated in 88% of women with

tecting ovarian cancer and generates a large proportion of false-positive results that often require diagnostic laparotomy or laparoscopy. In one study, ultrasound screening of 805 high-risk women led to 39 laparotomies, which revealed one ovarian carcinoma, two borderline tumors, one cancer of the cecum, and five cystadenomas.⁴⁰ A transvaginal ultrasound study of 600 patients with previous breast cancer revealed 18 patients with complex cysts or enlarged ovaries. Laparotomy was performed on 21 patients, four of whom had ovarian cancer (positive predictive value of 22%); the use of color-flow imaging appeared to increase the positive predictive value.⁴⁴

In a larger study, ultrasound was performed routinely on 5,678 asymptomatic female volunteers over age 45 or with a history of previous breast or gynecologic cancer.^{44a} Two Stage I ovarian cancers were detected in a total of 6,920 scans performed over 2 years. Another report from the same center indicated that 14,356 ultrasound examinations performed over 3 years on 5,489 asymptomatic women over age 45 detected five ovarian cancers.⁴⁵ Although the sensitivity and specificity of the test were excellent (100% and 94.6%, respectively), the positive predictive value in this low-risk study population was only 2.6% and follow-up was of short duration. It has been calculated from these results and other data that ultrasound screening of 100,000 women over age 45 would detect 40 cases of ovarian cancer, but at a cost of 5,398 false positives and over 160 complications from diagnostic laparoscopy.⁴⁶

It may be possible to improve accuracy by combining ultrasound with other screening tests, such as the measurement of CA-125. This approach has been examined as a method of discriminating between benign and malignant adnexal masses in preoperative patients.⁴⁷ Further research is needed, however, to determine the sensitivity, specificity, and positive predictive value of performing these tests in combination to screen asymptomatic women. One prospective study¹² screened 1,010 asymptomatic postmenopausal women over age 45 with pelvic examination and CA-125 measurement; those with abnormal results received an ultrasound examination. Although one ovarian cancer was detected (all three screening tests were positive in this woman), the study demonstrated poor positive predictive value with each of the three screening tests. No abnormality was discovered in 28 of the 31 women with elevated CA-125. Fibroids and benign cysts were responsible for over half of the 28 abnormal pelvic examinations. There were 13 abnormal ultrasound examinations; 12 of these women consented to laparotomy, which revealed six benign ovarian cysts, two fimbrial cysts, two women with no surgical findings, one woman with adhesions, and the ovarian cancer. A more recent report from the same center found that the combination of abdominal ultrasound and sequential CA-125 measurements had a sensitivity of 58–79%, a specificity of about 100%, and a positive predictive value of 27%.³¹ Another program

that screened 597 women with transvaginal color-flow Doppler ultrasound and CA-125 measurements detected abnormalities in 115 patients, only one of whom had ovarian cancer.⁴⁸

Effectiveness of Early Detection

There is no direct evidence from prospective studies that women with early-stage ovarian cancer detected through screening have lower mortality from ovarian cancer than do women with more advanced disease. A large body of indirect evidence, however, suggests that this is the case. Although lead-time and length biases may be responsible, it is known that survival from ovarian cancer is related to stage at diagnosis. The 5-year survival rate is 89% for localized disease, 36% for women with regional metastases, and 17% for women with distant metastases.⁴ Studies have shown that the most important prognostic factor in patients with advanced ovarian cancer is the size of residual tumor after treatment.^{4,7} Surgical debulking and chemotherapy for ovarian cancer appear to be more effective in reducing the size of residual tumor when ovarian cancer is detected early.⁴ Although these observations provide suggestive evidence that early detection may be beneficial, conclusive proof will require properly conducted prospective studies comparing long-term mortality from ovarian cancer between screened and nonscreened cohorts. A large clinical trial to obtain this evidence has recently been launched by the National Cancer Institute.⁴⁹ Under the most optimistic assumptions (100% sensitivity, 30% reduction in 5-year mortality with screening, no lead-time bias), annual pelvic examinations of 40-year-old women would reduce 5-year mortality from ovarian cancer in the population by less than 0.0001%.⁵⁰ Modeling studies that have examined annual CA-125 testing or a single screening with transvaginal ultrasound and CA-125 measurement have found that either approach would increase life expectancy by an average of less than 1 day per woman screened.^{51,52}

Recommendations of Other Groups

There are no official recommendations to screen routinely for ovarian cancer in asymptomatic women by performing ultrasound or serum tumor marker measurements. The American College of Physicians (ACP),⁵³ the Canadian Task Force on the Periodic Health Examination,⁵⁴ and the American College of Obstetricians and Gynecologists⁵⁵ recommend against such screening. A National Institutes of Health Consensus Conference on Ovarian Cancer recommended taking a careful family history and performing an annual pelvic examination on all women.⁵⁶ The pelvic examination, including palpation of the adnexae, is mentioned in a recommendation on Pap testing issued by the American Cancer Society, National Cancer Institute, American College of Obstetricians and Gynecologists,

American Medical Association, American Nurses Association, American Academy of Family Physicians, and the American Medical Women's Association.⁵⁷ Specifically, the pelvic examination (and Pap smear) is recommended annually for all women who are or have been sexually active or have reached age 18. Although Pap testing may be performed less frequently once three annual smears have been normal, the American Cancer Society specifies that the pelvic examination be performed with the Pap test every 1–3 years in women aged 18–40 years and annually thereafter.⁵⁸

The NIH Consensus Conference concluded that women with presumed hereditary cancer syndrome should undergo annual pelvic examinations, CA-125 measurements, and transvaginal ultrasound until childbearing is completed or at age 35, at which time prophylactic bilateral oophorectomy was recommended.⁵⁶ The ACP recommends counseling high-risk women about the potential benefits and harms of screening.⁵³ The Canadian Task Force on the Periodic Health Examination found insufficient evidence to recommend for or against screening for ovarian cancer in high-risk women.⁵⁴

Discussion

The sensitivity and specificity of available screening tests for ovarian cancer in asymptomatic women are uncertain and require further study. Although various tests can detect occasional asymptomatic tumors, there is currently no evidence that routine screening will improve overall health outcomes. The large majority of women with abnormal screening test results do not have cancer, yet will require invasive procedures (laparoscopy or laparotomy) to rule out malignancy. Given the risks, inconvenience, and substantial costs of follow-up testing, and the current lack of evidence that screening reduces morbidity or mortality from ovarian cancer, routine screening cannot be recommended. Trials to determine the benefits and risks of ovarian cancer screening are under way. There is also no evidence to support routine screening in women with a history of ovarian cancer in a first-degree relative. Although such women are at increased risk and stand to benefit more from interventions that reduce ovarian cancer mortality, the effectiveness of screening has yet to be determined for any group of women. Referral to a specialist may be appropriate for women whose family history suggests hereditary ovarian cancer syndrome, due to the very high risk of cancer in this disorder.

CLINICAL INTERVENTION

Screening asymptomatic women for ovarian cancer with ultrasound, the measurement of serum tumor markers, or pelvic examination is not recommended (“D” recommendation). There is insufficient evidence to rec-

ommend for or against the screening of asymptomatic women at increased risk of ovarian cancer (“C” recommendation).

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