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 III 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-

sidered a valid screening test for ovarian carcinoma.[16–18,21] Studies indicate that the Pap smear has a sensitivity for ovarian cancer of only 10–30%.[16]

Serum tumor markers are often elevated in women with ovarian cancer. Examples of these markers include carcinoembryonic antigen, ovarian cystadenocarcinoma antigen, lipid-associated sialic acid, NB/70K, TAG 72.3, CA15-3, and CA-125. CA-125 is elevated in 82% of women with advanced (Stage III or IV) ovarian cancer,[22] and it is also elevated, although less frequently, in women with earlier stage disease.[23] In studies of women with known or suspected ovarian cancer, the reported sensitivities of CA-125 in detecting Stage I and Stage II cancers are 29–75% and 67–100%, respectively.[24–30] These cases may not be representative of asymptomatic women in the general population, however. In screening studies, including a recent study of more than 22,000 women, the reported sensitivity was 53–85%.[13,31] Evidence is limited on whether tumor markers become elevated early enough in the natural history of occult ovarian cancer to provide adequate sensitivity for screening. Studies of stored sera have found that about one half of women who developed ovarian cancer had elevated CA-125 levels (>35 U/mL) 18 months[23] to 3 years[32] before their diagnosis. Further research is needed, however, to provide more reliable data on the sensitivity of this and other tumor markers in detecting early-stage ovarian cancer in asymptomatic women.

Tumor markers may have limited specificity. It has been reported that CA-125 is elevated in 1% of healthy women, 6–40% of women with benign masses (e.g., uterine fibroids, endometriosis, pancreatic pseudocyst, pulmonary hamartoma), and 29% of women with nongynecologic cancers (e.g., pancreas, stomach, colon, breast).[22,33] Reported specificity in screening studies is about 99%.[13,31] It may be possible to improve the specificity of CA-125 measurement by selective screening of postmenopausal women,[34] modifying the assay technique,[35] adding other tumor markers to CA-125,[36] requiring a higher concentration or persistent elevation of CA-125 levels over time, or combining CA-125 measurement with ultrasound (see below). Prospective studies involving asymptomatic women are needed, however, to provide definitive data on the performance characteristics of these techniques when used as screening tests.

Ultrasound imaging has also been evaluated as a screening test for ovarian cancer, since it is able to estimate ovarian size, detect masses as small as 1 cm, and distinguish solid lesions from cysts.[17,37] Transvaginal color-flow Doppler ultrasound can also identify vascular patterns associated with tumors.[38,39] In screening studies, the reported sensitivity and specificity of transabdominal or transvaginal ultrasound are 50–100% and 76–97%, respectively,[3,14,15,40–43] but small sample sizes, limited follow-up, and outdated techniques may limit the validity of the data. Studies have shown that routine ultrasound testing of asymptomatic women has a low yield in de-

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 study[12] 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.[1] 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 Gynecologists[55] 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 oopherectomy 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).

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Steven H. Woolf, MD, MPH, based in part on a paper prepared for the Clinical Efficacy Assessment Panel of the American College of Physicians by Karen J. Carlson, MD, et al. See relevant background paper: Carlson KJ, Skates SJ, Singer DE. Screening for ovarian cancer. Ann Intern Med 1994;121:124–132.

REFERENCES

1. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. CA Cancer J Clin 1995;45:8–30.

1a. Ries LAG, Miller BA, Hankey BF, et al, eds. SEER cancer statistics review, 1973–1991: tables and graphs. Bethesda: National Cancer Institute, 1994. (NIH Publication no. 94-2789.)

2. Pettersson F, ed. Annual report on the results of treatment of gynecologic cancer. Int J Gynecol Obstet 1991;36(suppl):238–277.
3. Goswamy RK, Campbell S, Whitehead MI. Screening for ovarian cancer. Clin Obstet Gynecol 1983;10:621–643.
4. Slotman BJ, Rao BR. Ovarian cancer: etiology, diagnosis, prognosis, surgery, radiotherapy, chemotherapy and endocrine therapy. Anticancer Res 1988;8:417–434.
5. Richardson GS, Scully RE, Nikrui N, et al. Common epithelial cancer of the ovary. N Engl J Med 1985;312:415–424.
6. Young RC. Ovarian cancer treatment: progress or paralysis. Semin Oncol 1984;11:327–329.
7. Young JL, Percy CL, Asire AJ, eds. SEER Program: incidence and mortality, 1973–1977. National Cancer Institute, Monograph 57. Washington, DC: Government Printing Office, 1981:75.
8. Whittemore AS, Harris R, Itnyre J, et al. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Am J Epidemiol 1992;136: 1184–1203.
9. Kerlikowske K, Brown JS, Grady DG. Should women with familial ovarian cancer undergo prophylactic oopherectomy? Obstet Gynecol 1992;80:700–707.
10. Amos CI, Struewing JP. Genetic epidemiology of epithelial ovarian cancer. Cancer 1993;71:566–572.
11. Biesecker B, Boehnke M, Calzone K. Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. JAMA 1993;269:1970–1974.
12. Jacobs I, Stabile I, Bridges J, et al. Multimodal approach to screening for ovarian cancer. Lancet 1988;1:268–271.
13. Einhorn N, Sjovall K, Knapp RC, Hall P, Scully RE, Bast RC, Zurawski VR. Prospective evaluation of serum CA 125 levels for the early detection of ovarian cancer. Obstet Gynecol 1992;80:14–18.
14. Van Nagell JR, DePriest PD, Puls NE, Donaldson ES, Gallion HH, Pavlik EJ, et al. Ovarian cancer screening in asymptomatic postmenopausal women by transvaginal sonography. Cancer 1991;68:458–462.
15. Andolf E, Jorgensen C, Astedt B. Ultrasound examination for detection of ovarian carcinoma in risk groups. Obstet Gynecol 1990;75:106–109.
16. Smith LH, Oi RH. Detection of malignant ovarian neoplasm: a review of the literature. 1. Detection of the patient at risk; clinical, radiological and cytological detection. Obstet Gynecol Surv 1984;39: 313–328.
17. Lynch HT, Albano WA, Lynch JF, et al. Surveillance and management of patients at high genetic risk for ovarian carcinoma. Obstet Gynecol 1982;59:589–596.
18. Hall DJ, Hurt WG. The adnexal mass. J Fam Pract 1982;14:135–140.
19. Griffiths CT. Carcinoma of the ovary and fallopian tube. In: Holland JF, Frei E, eds. Cancer medicine. Philadelphia: Lea & Febiger, 1982:1958–1969.
20. Graham JB, Graham RM, Schueller EF. Preclinical detection of ovarian cancer. Cancer 1964;17:1414.
21. Rubin P, Bennett JM. Ovarian cancer. In: Bakeman RP, ed. Clinical oncology for medical students and physicians: a multidisciplinary approach. 5th ed. New York: American Cancer Society, 1978:114–120.
22. Bast RC, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian carcinoma. N Engl J Med 1983;309:883–887.

23. Zurawski VR Jr, Orjaseter H, Andersen A, et al. Elevated serum CA 125 levels prior to diagnosis of ovarian cancer neoplasia: relevance for early detection of ovarian cancer. Int J Cancer 1988;42:677–680.
24. Zurawski VR Jr, Knapp RC, Einhorn N, et al. An initial analysis of preoperative serum CA 125 levels in patients with early stage ovarian carcinoma. Gynecol Oncol 1988;30:7–14.
25. Patsner B, Mann WJ. The value of preoperative serum CA 125 levels in patients with a pelvic mass. Am J Obstet Gynecol 1988;159:873–876.
26. Mogensen O, Mogensen B, Jakobsen A. CA 125 in the diagnosis of pelvic masses. Eur J Cancer Clin Oncol 1989;25:1187–1190.
27. Cruickshank DJ, Fullerton WT, Klopper A. The clinical significance of pre-operative serum CA 125 in ovarian cancer. Br J Obstet Gynaecol 1987;94:692–695.
28. Zanaboni F, Vergadoro F, Presti M, Gallotti P, Lombardi F, Bolis G. Tumor antigen CA 125 as a marker of ovarian epithelial carcinoma. Gynecol Oncol 1987;28:61–67.
29. Brioschi PA, Irion O, Bischof P, Bader M, Forni M, Krauer F. Serum CA 125 in epithelial ovarian cancer: a longitudinal study. Br J Obstet Gynaecol 1987;94:196–201.
30. Schilthuis MS, Aalders JG, Bouma J, et al. Serum CA 125 levels in epithelial ovarian cancer: relation with findings at second-look operations and their role in the detection of tumour recurrence. Br J Obstet Gynaecol 1987;94:202–207.
31. Jacobs I, Davies AP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. BMJ 1993;306:1030–1034.
32. Helzllsouer KJ, Bush TL, Alberg AJ, Bass KM, Zacer H, Comstock GW. Prospective study of serum CA125 levels as markers of ovarian cancer. JAMA 1993;269:1123–1126.
33. Di-Xia C, Schwartz P, Xinguo L, et al. Evaluation of CA 125 levels in differentiating malignant from benign tumors in patients with pelvic masses. Obstet Gynecol 1988;72:23–27.
34. Zurawski VR Jr, Broderick SF, Pickens P, et al. Serum CA 125 levels in a group of nonhospitalized women: relevance for the early detection of ovarian cancer. Obstet Gynecol 1987;69:606–611.
35. Klug TL, Green PJ, Zurawski VR Jr, et al. Confirmation of a false-positive result in CA 125 immunoradiometric assay caused by human anti-idiotypic immunoglobulin. Clin Chem 1988;34:1071–1076.
36. Jacobs IJ, Oram DH, Bast RC. Strategies for improving the specificity of screening for ovarian cancer with tumor-associated antigens CA125, CA15-3, and TAG 72.3. Obstet Gynecol 1992;80:396–399.
37. Campbell S, Goessens L, Goswamy R, et al. Real-time ultrasound for determination of ovarian morphology and volume: a possible early screening test for ovarian cancer? Lancet 1982;1:425–426.
38. Bourne T, Campbell S, Steer C, Whitehead MI, Collins WP. Transvaginal colour flow imaging: a possible new screening technique for ovarian cancer. BMJ 1989;299:1367–1370.
39. Kurjak A, Zalud I, Alfirevic Z. Evaluation of adnexal masses with transvaginal color ultrasound. J Ultrasound Med 1991;10:295–297.
40. Andolf E, Svalenius E, Astedt B. Ultrasonography for early detection of ovarian carcinoma. Br J Obstet Gynaecol 1986;93:1286–1289.
41. Campbell S, Royston P, Bhan V, Whitehead MI, Collins WP. Novel screening strategies for early ovarian cancer by transabdominal ultrasonography. Br J Obstet Gynaecol 1990;97:304–311.
42. Rodriguez MH, Platt LD, Medearis AL, Lacarra M, Lobo RA. The use of transvaginal ultrasonography for evaluation of postmenopausal size and morphology. Am J Obstet Gynecol 1988;159:810–814.
43. Bourne TH, Campbell S, Reynolds KM, et al. Screening for early familial ovarian cancer with transvaginal ultrasonography and colour flow imaging. BMJ 1993;306:1025–1029.
44. 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;12:387–393.

44a. Goswamy RK, Campbell S. Screening for ovarian cancer. IARC Sci Publ 1986;76:305–309.

45. Campbell S, Bhan V, Royston J, et al. Screening for early ovarian cancer. Lancet 1988;1:710–711.
46. Jacobs I. Screening for early ovarian cancer. Lancet 1988;2:171–172.
47. Finkler NJ, Benacerraf B, Lavin PT, et al. Comparison of serum CA 125, clinical impression, and ultrasound in the preoperative evaluation of ovarian masses. Obstet Gynecol 1988;72:659–664.
48. 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;169:494–501.
49. Kramer BS, Gohagan J, Prorok PC, Smart C. A National Cancer Institute sponsored screening trial for prostatic, lung, colorectal, and ovarian cancers. Cancer 1993;71:589–593.
50. Eddy DM. Annual pelvic examination. Ann Intern Med 1990;113:803.
51. Skates SJ, Singer DE. Quantifying the potential benefit of CA125 screening for ovarian cancer. J Clin Epidemiol 1991;44:365–380.

52. Schapira MM, Matchar DB, Young MJ. The effectiveness of ovarian cancer screening: a decision-analysis model. Ann Intern Med 1993;118:838–843.
53. American College of Physicians. Screening for ovarian cancer. Ann Intern Med 1994;121:141–142.
54. Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Canada Communication Group, 1994:869–881.
55. American College of Obstetricians and Gynecologists. Routine cancer screening. Committee Opinion no. 128. Washington, DC: American College of Obstetricians and Gynecologists, 1993.
56. National Institutes of Health. Ovarian cancer: screening, treatment, and follow-up. National Institutes of Health Consensus Conference Statement, April 5–7, 1994.
57. Fink DJ. Change in American Cancer Society checkup guidelines for detection of cervical cancer. CA Cancer J Clin 1988;38:127–128.
58. American Cancer Society. Guidelines for the cancer-related checkup: an update. Atlanta: American Cancer Society, 1993.