Screening for Ovarian Cancer

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■ *Purpose:* To critically review the available evidence for screening asymptomatic women for ovarian cancer with ultrasonography or the CA 125 radioimmunoassay (CA 125) or both.

■ *Data Sources:* A MEDLINE search of the English-language literature and bibliographies of published studies providing estimates of ovarian cancer risk and test operating characteristics (based on observational studies and meta-analyses) and effectiveness of treatment according to stage of disease (based on randomized trials). Published mathematical models simulating screening for ovarian cancer in specific populations were also included. Death from ovarian cancer and morbidity from surgical procedures were the principal outcomes considered.

■ *Results:* Age and family history are the most important risk factors for ovarian cancer. Annual screening with CA 125 or ultrasound in women older than 50 years without a family history of ovarian cancer would result in more than 30 false-positive results for every ovarian cancer detected. False-positive tests are likely to require invasive testing, often including laparotomy. There is currently no direct evidence that mortality from ovarian cancer would be decreased by screening.

■ *Conclusions:* Available evidence does not support either screening of pre- or postmenopausal women without a family history of ovarian cancer or routine screening in women with a family history of ovarian cancer in one or more relatives (without evidence of a hereditary cancer syndrome). Women from a family with the rare hereditary ovarian cancer syndrome are at high risk for the disease and should be referred to a gynecologic oncologist.

[Note that sections in this review are numbered so that they can be identified with cross-references as supporting evidence in the article "Screening for Ovarian Cancer: Recommendations and Rationale," published in the Clinical Guideline section of this issue; see pages 141-142.—The Editor]

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1. Ovarian cancer is the most frequent cause of death from gynecologic malignancy in the United States, accounting for approximately 12 500 deaths annually (1). Breast cancer and cervical cancer, other cancers in women for which screening programs currently exist, cause approximately 43 000 and 4 000 deaths per year, respectively (1).

1.1 Ovarian cancer has spread beyond the ovary by the time of clinical detection in 75% of patients (2). Five-year survival in such patients is less than 35%. Five-year survival in patients with stage I disease has been more than 70% in older case series and recently has been reported to be more than 90% (2–5). Despite new treatment regimens, mortality from ovarian cancer has decreased only slightly in the past 30 years (6). Although advances in treatment may ultimately improve the outcome of clinically diagnosed ovarian cancer, early detection through screening has become an attractive approach to decreasing mortality from this disease.

1.2 Does current scientific evidence justify screening asymptomatic women for ovarian cancer? We review the epidemiology of ovarian cancer, consider the potential benefits and risks of screening, evaluate available screening techniques, and address the effectiveness of specific screening programs. We provide specific recommendations about current techniques for screening for ovarian cancer and provide a framework for evaluating future techniques for screening.

2. Methods

Relevant articles from the medical literature were identified using a MEDLINE search (1982 to the present) of English-language articles or articles with English abstracts, the bibliographies of articles retrieved, and the authors' files. The selection of articles on risk factors for ovarian cancer was limited to formal epidemiologic studies of defined populations. The selection of articles on the effectiveness of treatment included randomized trials and case series. Sources of data on the sensitivity and specificity of screening techniques were case series and randomized trials. When calculating summary estimates of sensitivity and specificity, we included only studies that had operative confirmation of ovarian cancer and that provided sufficient primary data to determine test operating characteristics in a defined population. For studies of the CA 125 radioimmunoassay, calculations of summary estimates were based on studies that reported data allowing calculation of test operating characteristics using the widely accepted reference level of 35 U/mL. A mathematical model of screening using CA 125 presented here includes unpublished data obtained from the work of Einhorn and colleagues (7) and from our own work in determining the medical care costs associated with ovarian cancer (Carlson KJ. Unpublished observations.).

3. Epidemiology of Ovarian Cancer

3.1 Pathology

The World Health Organization Classification of ovarian tumors defines various tumor types on the basis of

histologic criteria. Common epithelial tumors account for 90% of all ovarian malignancies (8). This category contains various cell types, including serous, mucinous, endometrioid, and clear cell tumors. A subgroup of epithelial neoplasms, termed "borderline tumors" or "cystadenomas of low malignant potential," have a much less aggressive course. Finally, the common epithelial tumors include benign cystadenomas. Malignant transformation of benign cystadenomas has been reported (9), and women with a family history of ovarian cancer have been found to have a higher prevalence of serous cystadenomas and other benign tumors than women without such a history (10–12). The probability of malignant transformation is unknown; therefore, the magnitude of any benefit in identifying asymptomatic benign cystadenomas for prevention of future ovarian malignancy is not known.

3.2 Incidence

The incidence of ovarian cancer in the United States is reported as approximately 20 700 patients per year (1). The annual incidence increases with age, from approximately 20 per 100 000 in women aged 30 to 50 years to 40 per 100 000 in women aged 50 to 75 years (1). The mean age at clinical presentation in the general population is 59 years. The lifetime probability of developing ovarian cancer is 1 in 70.

3.3 In estimating potential benefits of screening for ovarian cancer, it is important to consider the effect of previous oophorectomy on published incidence rates (13). Screening programs are appropriately targeted only to women with at least one ovary, and a substantial number of women in the United States have already had oophorectomy (often accompanying hysterectomy) by the time they reach middle age. In women 50 to 75 years old, adjusting for previous oophorectomy increases the annual incidence to approximately 50 per 100 000 in women with at least one ovary (compared with an unadjusted incidence of 40 per 100 000).

3.4 Estimating the Risk for Ovarian Cancer

Because the incidence of ovarian cancer increases with age, screening programs would be more efficiently focused on older women. Knowledge of other risk factors could also be used to target screening programs toward populations at highest risk.

3.5 The strongest risk factor for ovarian cancer identified to date is familial evidence of ovarian cancer, which is reported in about 7% of women with the disease (14). There are two types of familial patterns for ovarian cancer: 1) Hereditary ovarian cancer syndromes refer to a pattern of clusters of ovarian cancer (site-specific ovarian cancer syndrome); ovarian and breast cancer (breast-ovarian cancer syndrome); or nonpolyposis colorectal cancer, endometrial cancer, and ovarian cancer (the Lynch II syndrome) within two or more generations of a kindred (15); 2) a "family history of ovarian cancer" pertains to women whose families include isolated women with ovarian cancer, often only one relative, without evidence of a hereditary pattern. Differentiating these two groups is important for efforts that target any screening program to populations at greatest risk because the risk for cancer in each group appears to differ substantially.

3.6 Hereditary ovarian cancer syndromes account for a small number of patients with ovarian cancer. Although the exact proportion of women with the hereditary syndromes is unknown, it is estimated that they account for less than 1% of women with ovarian cancer and less than 3% of cancer among women with familial evidence of ovarian cancer (16). Although the risk for ovarian cancer in a woman belonging to a kindred with a hereditary ovarian cancer syndrome cannot be precisely determined because of the small number of reported cases, it is clear that in some women the risk may be very high. An autosomal dominant mode of inheritance has been shown in some families, which may confer a lifetime probability of developing ovarian cancer of up to 50% (15–20). Thus, women from families with hereditary ovarian cancer syndromes constitute the group at highest known risk and the group at highest priority for any preventive interventions.

3.7 Clues to the presence of a hereditary ovarian cancer syndrome include the occurrence of ovarian or related cancers in multiple members of two to four generations of the family (17) and include presentation of ovarian cancer at an earlier age (average ages at presentation for the three syndromes range from 45 to 52 years compared with the general population average age of 59 years) (18, 19). These clues, if present, may alert the primary physician to the possibility of a hereditary ovarian cancer syndrome; referral to a geneticist for further evaluation and determination of family pedigree is then appropriate. However, detailed family histories may not be available for many patients.

3.8 A family history of ovarian cancer in a first- or second-degree relative is much more common than the hereditary syndromes. Seven percent of women with ovarian cancer report a family history of the disease; more than 90% of these women have a single relative with ovarian cancer (14, 16). The magnitude of risk associated with a family history of ovarian cancer has been evaluated in 10 published case-control studies (14, 21–29). The relative risk estimates reported in these studies vary widely, ranging from a 2-fold to an 18-fold increase in baseline risk.

3.9 Kerlikowske and colleagues (16) derived pooled estimates of the relative risk for ovarian cancer by combining data from 7 of the 10 studies meeting specific methodologic criteria. For women with one affected relative (first- or second-degree), the estimated odds ratio for ovarian cancer was 3.1 (95% CI, 2.2 to 4.4); for women with two or three affected relatives, the odds ratio was 4.6 (CI, 1.1 to 18.4). A similar analysis of pooled data restricted to U.S. case-control studies found a 3.6-fold increase in risk associated with any family history of ovarian cancer (30). These analyses provide the best available information on the magnitude of risk associated with a family history of ovarian cancer and indicate a modest increase in absolute risk. Using the relative risks reported by Kerlikowske and colleagues (16), we can estimate that a family history of ovarian cancer in one relative increases the lifetime probability of ovarian cancer in a 50-year-old woman from 1.2% to 3.7%, and to 5.5% in a woman having two or three relatives with ovarian cancer.

Table 1. Risk Factors for Ovarian Cancer

Risk Factor	Relative Risk	Lifetime Risk for Ovarian Cancer, %*
No risk factors	1.0	1.2
Familial ovarian cancer syndrome	Unknown	Up to 50
One first- or second-degree relative with ovarian cancer	3.1†	3.7
Two or 3 relatives with ovarian cancer	4.6†	5.5
Oral contraceptive pill use	0.65‡	0.8
Pregnancy	0.5§	0.6

* Risk for cancer in a 50-year-old woman. Calculated from relative risk estimates and ovarian cancer incidence data from the SEER (Surveillance, Epidemiology, and End-Result) Program (1). Calculations assume that a family history of ovarian cancer is relatively uncommon.
† Based on reference 16.
‡ Based on references 31 and 32.
§ Based on reference 31.

3.10 Two other factors have been consistently shown to modify the risk for ovarian cancer. Use of the oral contraceptive pill appears to decrease the risk for ovarian cancer. Whittemore and colleagues (31) analyzed data combined from 12 case-control studies and Hankinson and colleagues (32) used pooled data from 20 published studies to derive summary estimates of the risk associated with contraceptive pill use; both found similar relative risks of approximately 0.65 associated with any use of the pill. Increasing duration of oral contraceptive pill use is associated with a decreased risk for ovarian cancer; both studies found a relative risk of approximately 0.5 after 5 years of use.

3.11 Parity has also been clearly associated with a decreased risk for ovarian cancer. Whittemore and colleagues (31) analyzed combined case-control data and found a risk reduction of approximately 50% (that is, a relative risk of 0.5) for any pregnancy, with decreasing risk associated with an increasing number of pregnancies. Breast-feeding was associated with a 20% decrease in risk (31). Other reproductive and environmental risk factors have been studied, but none has shown a consistent and substantial effect on risk for ovarian cancer. These include menstrual history, age at first pregnancy, infertility, hormonal replacement therapy, and dietary factors.

3.12 Table 1 summarizes the best available information on risk factors for ovarian cancer. Women with a family history of a hereditary ovarian cancer syndrome represent a small subgroup that is at highest risk, with a lifetime probability of ovarian cancer of up to 50%. Women with a family history of ovarian cancer in one or more relatives (without evidence of a hereditary pattern) have a threefold increase in risk. Familial evidence of ovarian cancer, age, use of the oral contraceptive pill, and parity should be considered when assessing an individual woman's risk for ovarian cancer. Interactions between family history and oral contraceptive pill use or parity have not been well quantified (30).

4. Benefits and Risks of Screening

4.1 Potential Benefits

Ovarian cancer is often asymptomatic until it has disseminated. In 75% of patients with ovarian cancer, the tumor has spread beyond the ovary at the time of clinical diagnosis (Table 2), resulting in an overall 5-year survival of 28% to 35% (2, 33, 34). In contrast, the 5-year survival in patients with stage I disease (localized to the ovary) has ranged from 66% to 80% in published case series (Table 2). Five-year survival of more than 90% has recently been reported in women with stage I ovarian cancer treated with surgery and a single alkylating agent (4, 5).

4.2 The benefit of screening lies in its potential to shift diagnosis to a more localized and curable stage. No randomized controlled trials of any ovarian cancer screening method have been done to determine whether earlier diagnosis and decreased mortality (compared with no screening) could be achieved. In the absence of a controlled trial showing that screening leads to a decrease in population rates of death caused by ovarian cancer, estimates of the benefits of screening are tentative at best.

4.3 To estimate the stage shifts that could result from screening, we need to know the stage progression over time of ovarian cancer, that is, its natural history. However, little is known about the natural time course of progression from localized to disseminated stages because therapy is nearly always begun at diagnosis. Although a model of disease progression from localized through disseminated stages is plausible, it is unproved. Indeed, there are women who develop ovarian carcinomatosis after the removal of normal ovaries, suggesting that some ovarian cancers develop from Müllerian rests outside the ovary (35). As a practical matter, models of screening may assume that patients with cancer detected by screening have the same survival distribution as those with cancer detected clinically in the same stage. There is no empiric evidence to support this assumption.

4.4 Potential Risks

The main benefit of screening, an increased survival for women who have ovarian cancer, must be weighed against adverse effects of screening borne by women who do not have ovarian cancer, principally those who falsely test positive in the screening program. Although ovarian cancer is an important cause of cancer mortality, its incidence and prevalence are relatively low. With such a low prevalence of undetected disease, the problem of false-positive tests becomes potentially very important (36). A

Table 2. Stage at Clinical Presentation and Mortality from Ovarian Cancer

Stage	Definition	Patients in Stage at Clinical Detection*	Five-year Survival†
		%	
I	Confined to ovaries	25	73
II	Extension within pelvis	8	45
III	Intraperitoneal metastases outside pelvis or positive retroperitoneal nodes	52	21
IV	Distant metastases	15	17

* Derived from references 2, 43, 53, 54, and 72.
† Derived from references 2 and 3.

Table 3. Sensitivity and Specificity of Ultrasound for the Detection of Ovarian Cancer

Study (Reference)	Total	Women with Cancer	Sensitivity, All Stages Combined	Specificity
	n		%	
Studies in women with known or suspected ovarian cancer				
Abdominal ultrasound				
Finkler et al. (42)	131	37	62	
Benacerraf et al. (45)	100	30	80	
Requard et al. (46)	32	32	88	
Herrmann et al. (47)	312	50	92	
Luxman et al. (48)	102	29	93	
Transvaginal ultrasound				
Granberg et al. (49)	180	38	82	
Sassone et al. (43)	143	11	100	
Screening studies				
Abdominal ultrasound				
Andolf et al. (51)	805	3	100	95.5
Andolf et al. (40)	801	1	100	75.5
Goswamy et al. (3)	1077	1	100	96.9
Campbell et al. (11)	5479	5*	100	94.0
Transvaginal ultrasound				
Van Nagell et al. (12)	1300	2*	100	97.6
Rodriguez et al. (50)	52	2	50	76.0
Bourne et al. (52)	1601	6†	100	96.6
Summary estimate (95% CI)‡	11 115	247	85 (80 to 90)	93.8 (93.3 to 94.3)

* All patients had stage I ovarian cancer.
† Five of six patients had stage I ovarian cancer.
‡ Summary estimates were calculated as an average weighted estimate according to sample size.

false-positive test result falsely indicates that ovarian cancer is present when in fact it is absent.

4.5 The adverse clinical consequences of false-positive tests are considerable; evaluation of a woman suspected of having ovarian cancer because of a positive screening test will likely lead to laparotomy, the standard operative approach for evaluation of suspected ovarian cancer (37, 38). Limited data support the use of laparoscopy as an alternative to laparotomy in selected women with adnexal masses (39).

5. Available Screening Techniques

5.1 Pelvic Examination

The pelvic examination, although useful in early detection of other gynecologic cancers, is of limited value in screening asymptomatic women for ovarian cancer. In general, ovarian malignancies have disseminated by the time they are palpable, and standard clinical teaching views the pelvic examination alone as an ineffective method of screening (8). Formal evaluation of the sensitivity and specificity of bimanual examination has been limited to four studies that combined physical examination with other screening modalities. Pelvic examination failed to detect either of the two tumors (stage I) found in the study by van Nagell and colleagues (12) of transvaginal ultrasound and did not detect the single cancer (a borderline tumor) found by abdominal ultrasound in the study by Andolf and coworkers (40). In a study of multiple screening techniques, Jacobs and colleagues (41) reported a single ovarian cancer (stage I); it was palpable on examination. Finally, five of six patients whose ovarian cancers (stages I, II, and III) were detected in Einhorn's screening study (7) were associated with abnormal pelvic examinations. Some of these studies suggest that a pelvic examination by a highly skilled examiner may show early-stage ovarian cancer. It is reasonable to examine the ovaries at the time of pelvic examination done for cervical cancer screening or other clinical reasons, recognizing that limited scientific evidence supports its use solely to screen for ovarian cancer.

5.2 Ultrasound and Other Imaging Techniques

Early studies of ultrasound used transabdominal sonography; more recently, transvaginal sonography has also been evaluated as a screening method, along with color-flow Doppler techniques to improve specificity. No universally accepted criteria exist for the sonographic diagnosis of ovarian cancer, although scoring systems featuring explicit and reproducible criteria have been developed (42–44). The studies summarized here reflect a spectrum of systems, implicit and explicit, for classifying an ultrasound examination as suggestive or indicative of malignancy.

5.3 Estimates of the sensitivity of ultrasound and other screening tests for ovarian cancer can be derived from two sources. The first is studies of women with known or suspected ovarian cancer who have had the test before surgery. The second source, studies of the test's performance in screening asymptomatic women for ovarian cancer, is the ideal basis for estimating sensitivity. However, screening studies usually feature a small number of patients with ovarian cancer (limiting the precision of sensitivity estimates) and a short follow-up period (leading to overestimates of sensitivity). The former type of study provides more patients with cancer, allowing more precise estimates of sensitivity; however, the patients generally have later-stage cancer, which tends to overestimate sensitivity.

5.4 Table 3 summarizes data on the sensitivity of ultrasound for detection of ovarian cancer. Studies of women with known or suspected ovarian cancer have shown sensitivities ranging from 80% to 100% for transabdominal and transvaginal ultrasound (42, 43, 45–49). These studies do not report information on the sensitivity of ultrasound for detection of stage I and stage II disease. The sensitivities reported in screening studies have been much higher: six of seven studies reported sensitivities of 100% (3, 11, 12, 40, 50–52). In the three studies describing the stage at diagnosis, 12 of 13 patients had stage I cancer (11, 12, 52). Although these findings indicate that transabdominal and transvaginal ultrasound have the potential to detect early-stage disease, the small numbers and limited extent of follow-up must be taken into account.

5.5 Screening studies are the only appropriate source of estimates of the specificity of ultrasound or other screening tests. Specificity estimates from screening studies of ultrasound (Table 3) range from 76% to approximately 97%, with transvaginal ultrasound reaching the highest specificity at 97.6%.

5.6 Table 3 includes our summary estimates of the sensitivity and specificity of ultrasound, calculated by combining published values using an average weighted on the basis of sample size. The summary estimate of the sensitivity of ultrasound for detection of cancer is 85% and the specificity is 93.8%.

5.7 Color-flow Doppler techniques to detect tumor neovascularization have been studied (53) in efforts to improve the specificity of transvaginal ultrasound. Malignant tumors typically show vessels with high velocity and low impedance flow characteristics. Two studies (53, 54) have found improvements in the specificity of ultrasound when combined with the color-flow Doppler technique. With the limited nature of available data, color-flow Doppler is best viewed as a promising but unconfirmed adjunct procedure in any screening program incorporating ultrasound.

5.8 Ultrasound has no known hazards. The main disadvantages of ultrasound as a screening method are the time, equipment, and personnel required to do the examination.

5.9 CA 125 and Other Tumor Markers

CA 125 is an antigenic determinant on a glycoprotein that is shed into the bloodstream by malignant cells derived from coelomic epithelium (that is, Müllerian ducts and cells lining the peritoneum, pleura, and pericardium) (55). Serum levels of CA 125 are increased in approximately 80% of patients with epithelial ovarian cancers; they are more frequently increased in patients with the nonmucinous histologic types. Levels of CA 125 are also increased in patients with advanced endometrial cancers and in about 60% of those with pancreatic cancers. They are sometimes increased in patients with certain benign gynecologic conditions (including endometriosis, uterine leiomyoma, pelvic inflammatory disease, early pregnancy, and benign ovarian cysts) and in those with cirrhosis and pericarditis (55).

5.10 Serum levels of CA 125 have been shown to fluctuate during the menstrual cycle (56). Screening with CA 125 in premenopausal women has been little studied, owing to the difficulties posed by menstrual cycle variation and by the relatively high prevalence of benign gynecologic conditions associated with increased levels of CA 125 in the premenopausal population.

5.11 Information on the sensitivity of the CA 125 radioimmunoassay in screening women for ovarian cancer can be drawn from studies of its performance in women with known ovarian cancer and from screening studies (Table 4). For a reference level of 35 U/mL, the sensitivity of the CA 125 radioimmunoassay observed in published studies (42, 57–72) of women with clinically diagnosed ovarian cancer ranges from 61% to 96%. The reported sensitivity for detecting stage I disease ranges from 25% to 75% and for stage II disease from 67% to 100%.

5.12 The sensitivity of the CA 125 radioimmunoassay in a screening setting is also of interest, although the small numbers of cancers detected in such studies result in less precise estimates of sensitivity (7, 73, 74). Two large screening studies in postmenopausal women have been done. In a Swedish trial (7) of two consecutive annual screenings with the CA 125 radioimmunoassay in more than 5000 women, 6 women eventually developed clinically diagnosed ovarian cancer. Four of 6 had CA 125 levels greater than 35 U/mL on the first screen, and all 6 were above 35 U/mL on the second screen. Because the time at which the tumors arose and were potentially detectable cannot be known, the apparent sensitivity of CA 125 in this study ranges from 67% to 100%. The largest published series (74), done in England, screened 22 000 postmenopausal women with a single CA 125 level. For a reference level of 35 U/mL, the apparent sensitivity ranged from 53% to 89% (74).

5.13 Two studies (75, 76) of CA 125 levels in serum banks also provide relevant data on sensitivity. Levels of CA 125 greater than 35 U/mL were shown 18 months before clinical detection in one third of women (4 of 12) subsequently diagnosed with ovarian cancer (75). Another study (76) reported CA 125 levels greater than 35 U/mL within 3 years before clinical diagnosis in 4 of 7 (57%) patients with ovarian cancer.

5.14 Estimates of the specificity of the CA 125 radioimmunoassay must be derived from community screening studies. Table 4 shows the specificity of the CA 125 radioimmunoassay based on data from the three published screening studies. The earliest study (69), one in which 1082 Swedish women were screened with a single CA 125 assay, reported a specificity of 99.4% in postmenopausal women (using a reference level of 35 U/mL). The specificity achieved by redefining a positive test as a CA 125 level greater than 35 U/mL that doubles within 6 months was 99.9% (lower 95% CI, 99.5%). A larger Swedish study (7) of screening using two consecutive annual CA 125 assays in 5550 women reported a specificity for a single CA 125 level of 99.0% in women aged 50 years and older. Finally, the largest screening study (74) to date, one in which 22 000 postmenopausal women were screened with a single CA 125 assay, reported a specificity of 98.6% using a reference level of 30 U/mL.

5.15 The effect of combining CA 125 with ultrasound was also evaluated in the British screening study (74). A screening protocol of sequential CA 125 and transabdominal ultrasound (which defined a positive screening result

Table 4. Sensitivity and Specificity of the CA 125 Radioimmunoassay for the Detection of Ovarian Cancer*

Study (Reference)	Total, *n*	Women with Cancer, *n*	Sensitivity, %			Specificity, %
			All	Stage I	Stage II	
Studies in women with known or suspected ovarian cancer						
Einhorn et al. (57)	18	18	61			
O'Connell et al. (58)	56	38	95			
Malkasian et al. (59)	158	68	78			
Vasilev et al. (60)	182	18	78			
Finkler et al. (42)	106	37	68			
Chen et al. (61)	255	58	72			
Einhorn et al. (62)	219	54	81			
Soper et al. (63)	100	54	85			
Maggino et al. (64)	76	34	88			
Yedema et al. (65)	70	38	71			
Patsner et al. (66)	250	128	72	29	100	
Mogensen et al. (67)	184	118	82	61	67	
Cruickshank et al. (68)	41	41	73	25	67	
Zurawski et al. (69)	36	36	61	50	83	
Zanaboni et al. (70)	57	57	75	53	75	
Brioschi et al. (71)	69	69	84	31	100	
Schilthuis et al. (72)	46	46	96	75	100	
Screening studies						
Zurawski et al. (73)	1 082	1	100			99.4
Einhorn et al. (7)†	5 550	6	67			99.0
Jacobs et al. (74)‡	22 010	19	53			98.8
Summary estimate (95% CI)§	28 632	931	78 (73 to 83)	46	92	98.9 (98.6 to 99.2)

* Reference level is 35 U/mL for the CA 125 radioimmunoassay.
† See text for discussion of the apparent sensitivity in this study. Two patients had stage I cancer, two had stage II, and two had stage III at the time of clinical detection.
‡ Three patients had stage I cancer, one had stage II, six had stage III, and two had stage IV.
§ Summary estimates were calculated as an average weighted estimate according to sample size.

as a CA 125 level greater than 30 U/mL and an abnormal ultrasound test result) yielded a specificity of 99.9% and an apparent sensitivity of 58% to 79%. Addition of the tumor markers CA 15-3 or TAG 72.3 to CA 125 has also been shown to improve specificity (77). Other tumor markers, including lipid-associated sialic acid in plasma (LSA) and NB/70K, are being investigated as primary or secondary screening methods (78).

6. The Potential Yield of Screening with Ultrasound or CA 125

6.1 The available data on the prevalence of ovarian cancer, risk factors, and operating characteristics of ultrasound and CA 125 permit estimation of the potential yield of screening with either test. As we have outlined above, achieving a sufficiently high predictive value from a positive screening test is a critical factor in screening for ovarian cancer, given the relative rarity of the disease and the necessity for invasive procedures to evaluate a positive screening test. Table 5 shows the range of positive predictive values resulting from a hypothetical screening program with either ultrasound or CA 125 done annually in women 50 years of age and older classified according to the presence of the single strongest risk factor, familial evidence of ovarian cancer. The predictive values are calculated using our summary estimates for sensitivity and specificity from pooled published data (summarized in Tables 3 and 4) and prevalence estimates from national cancer surveillance statistics (1), adjusted for previous oophorectomy.

6.2 The positive predictive values calculated here represent the probability that ovarian cancer at any stage will be present if the screening test is positive. Whether screen detection would result in a decrease in mortality is unknown. The optimal threshold positive predictive value for any ovarian cancer screening protocol is undefined. Some have suggested that a positive predictive value less than 10% would be unacceptable in clinical practice (74).

6.3 For ultrasound, the predictive value of an abnormal test is less than 1% for women at average risk and is 2% for women with a history of ovarian cancer in one relative. Screening women at average risk using CA 125 also results in a low predictive value of 3%. For women with one or more relatives having ovarian cancer, a predictive value of 10% could theoretically be attained with CA 125 alone. In our view, these predictive values are too low to justify routine screening with either CA 125 or ultrasound, particularly in the absence of any data documenting a decrease in mortality because of screening.

6.4 In clinical practice, any screening test is likely to be used serially or in combination with other tests. The screening protocol evaluated in the British study by Jacobs and colleagues (74), who used CA 125 as the primary screening test followed by ultrasound for those with abnormal CA 125 values, achieved a positive predictive value of 27%. Other strategies could improve the predictive value of screening with CA 125. These include increasing the reference level, for example, from 35 U/mL to 95 U/mL. Although this approach increases specificity, it also decreases sensitivity, resulting in an improved positive predictive value but with fewer patients with cancer detected overall. In the large Swedish screening study (7),

Table 5. Predictive Value of Annual Screening with Ultrasound or CA 125 in Women 50 Years of Age and Older*

Screening Method	Screened Population	
	Women at Average Risk	Women with One Relative with Ovarian Cancer
Ultrasound†		
Predictive value of a positive test, %	0.7	2
CA 125‡		
Predictive value of a positive test, %	3	10

*Prevalence at annual screen = 0.0005. Prevalence is calculated from SEER (Surveillance, Epididemiology and End-Result) Program data (1), adjusted for previous oophorectomy by the method of Howe (13).

† Sensitivity, 85%; specificity, 93.8%. See Table 3 for source of sensitivity and specificity estimates.

‡ Sensitivity, 78%; specificity, 98.9%.

using 95 U/mL as the reference level increased specificity to 99.9% but decreased apparent sensitivity from 100% to 67%, increasing the positive predictive value from 13% to 50% (7). Another approach, which looks at the pattern over time for a person's results, might define a positive test as a CA 125 level greater than 35 U/mL that either persists or increases during a given time period. For example, it appears that requiring a doubling during 6 months of a level that is initially 35 U/mL or higher raises specificity to 99.9% (73). Methods for improving the sensitivity and specificity of ultrasound are under evaluation; these include color-flow Doppler imaging and scoring systems for defining an abnormal ultrasound result (44, 53). Studies now in progress to assess combinations of tests should provide useful information on the yield of these screening approaches. Determination of the potential for decreasing ovarian cancer mortality by screening requires a randomized trial. The National Cancer Institute plans a trial of screening for ovarian cancer in women aged 60 to 74 years using CA 125, transvaginal sonography, and physical examination (79).

7. Models of the Effectiveness of Ovarian Cancer Screening

In the absence of data from a randomized trial, mathematical models have been used to estimate the potential years of life that might be saved by screening for ovarian cancer using CA 125 alone or combined with transvaginal sonography (80, 81). We constructed a formal mathematical model of the natural history of ovarian cancer using a stochastic progression across the four clinical stages (80). The fundamental underlying assumption in this model is the expected duration of early-stage disease. The results presented here, which assume that the duration of stage I is 9 months, are given to show the potential benefit that could accrue with annual CA 125 screening; results assuming variation in the duration of stage I from 1 month to 3 years are presented elsewhere (80). Although the duration of stage I disease is an unobservable variable, other empirical evidence realistically defines the model. The distribution of CA 125 levels at clinical diagnosis for each stage, the stage distribution of ovarian cancer at clinical diagnosis, and the exponential increase of CA 125 in occult ovarian cancer have all been well documented and are represented in the model.

7.1 A computer simulation of the model was used to estimate the expected benefits of screening one million postmenopausal women aged 50 to 75 years with an annual CA 125 assay. The model assumed a strategy of laparotomy for all women with a single CA 125 test result above 35 U/mL. The results of the computer simulation indicated that almost three fifths (59.2%) of all cases would be detected by screening and that 75% of cases detected by screening would be identified at an earlier stage (compared with no screening). Averaging over all stages, the years of life saved per case of ovarian cancer equalled 3.4 years. This model has also been used to estimate the cost per year of life saved by an annual screening program in women older than 50 years using CA 125. The cost per year of life saved ranged from $95 000 to $36 000 for CA 125 test specificity varying from 99.0% to 99.8% (Carlson KJ. Unpublished observations).

7.2 Another model of ovarian cancer screening used decision analysis to compare no screening with a one-time screen with CA 125 and transvaginal sonography in 40-year-old women (81). In this population, a single screening with the combined tests was estimated to increase average life expectancy in the population by less than 1 day. A similar increase in average life expectancy was estimated for a cohort of 65-year-old women. This model reflects the adverse effect of laparotomy-related deaths in the screened population.

8. Official Recommendations for Screening

Several professional organizations have issued official recommendations on screening for ovarian cancer. The U.S. Preventive Services Task Force used formal literature review and explicit criteria in formulating screening recommendations (82). Their 1989 report stated: "Screening of asymptomatic women for ovarian cancer is not recommended. It is clinically prudent to examine the uterine adnexa when performing gynecologic examinations for other reasons." In the same year, the American College of Obstetricians and Gynecologists issued a report (83) from its Task Force on Routine Cancer Screening stating that routine screening for ovarian cancer using currently available techniques (other than the pelvic examination) was not recommended. The American Cancer Society recommends periodic pelvic examinations and has published no other specific recommendations for ovarian cancer screening.

9. Conclusions

Although the dismal prognosis of clinically detected ovarian cancer has prompted growing interest in screening as a means of decreasing mortality from this disease, clinical studies about screening are currently limited. Epidemiologic studies have identified age and a family history of ovarian cancer as the most important risk factors. These risk factors could be used to identify subpopulations of patients who would receive the greatest potential benefit from screening.

9.1 Clinical studies of screening methods have focused on two tests: ultrasound (transabdominal or transvaginal) and the CA 125 radioimmunoassay. Ultrasound (either transabdominal or transvaginal) is not suitable as a single primary screening test for women at average risk because its predictive value is very low. CA 125 shows promise as a screening test that may be simpler, less expensive, and more specific than ultrasound, but empiric evidence is too limited to justify its use for routine screening of women at average risk. No randomized controlled trials exist to show whether screening with CA 125 or ultrasound decreases mortality from ovarian cancer.

10. Recommendations

1. For pre- and postmenopausal women without a family history of ovarian cancer, screening for ovarian cancer with ultrasound or CA 125 is not currently recommended.

2. In women with a family history of ovarian cancer in one or more relatives (without evidence of a hereditary cancer syndrome), routine screening with CA 125 or ultrasound in general is not recommended. Women requesting screening should be counseled about their individual risk (considering age, parity, and history of oral contraceptive pill use), about the potential adverse effects of screening, and about the lack of scientific evidence that deaths from ovarian cancer are decreased by screening. Women and their physicians should consider this information when making individual decisions about screening.

3. For women from a family with the rare hereditary ovarian cancer syndrome, referral for specialist care is recommended.

Early detection of ovarian cancer through screening remains an attractive strategy for improving outcome from this disease. The time is right for a research program assessing whether tumor markers and advanced imaging techniques are effective and efficient screening tests for ovarian cancer.

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