Controversies in Cancer Prevention and Screening
Judith M. E. Walsh, MD, MPH

ABSTRACT

It is generally agreed that a cancer screening test should be offered to an entire population if the test reduces mortality due to that type of cancer. However, controversies regularly erupt about which tests are most beneficial, how often they should be performed, and at what age screening can be discontinued. This article reviews evidence pertaining to current controversies about screening for colon, cervical, breast, ovarian, and lung cancer.

Screening for colorectal cancer has been shown to reduce mortality, and several professional organizations recommend that all individuals older than 50 years of age be screened. However, no evidence conclusively shows which screening test is superior. Virtual colonoscopy and fecal DNA testing may have a future role but are not yet ready for routine use. Screening for cervical cancer can be discontinued in patients older than 65 or 70 years of age if the woman has consistently had normal Papanicolaou (Pap) smears and is not at high risk. Human papillomavirus typing is not recommended for routine screening in women at average risk for cervical cancer. Mammography screening for breast cancer is clearly beneficial for women aged 50 to 69 years, and physicians should discuss the pros and cons of mammography with women aged 40 to 49 years, as well as those aged 70 years or older. Screening for ovarian cancer is not recommended for women who are at average risk, but the serum CA-125 assay, rectovaginal pelvic examination, and transvaginal ultrasound may be considered for high-risk patients. No evidence demonstrates that screening for lung cancer reduces mortality.


PRINCIPLES OF SCREENING

Screening for the early detection of cancer has been associated with decreased morbidity and mortality from several cancers and is an important part of primary care practice, although several controversies about cancer screening remain. When making decisions about screening, characteristics of the disease and of the screening test must be considered. These characteristics determine whether screening for a particular disease is appropriate:

• The disease should have a high prevalence among those screened.
• It should have serious consequences.
• It should have a detectable preclinical phase.
• The disease should have a treatment that, when applied to presymptomatic disease, is more effective than if applied after symptoms develop.
• The tests used should be simple, inexpensive, and acceptable, with high degrees of sensitivity and specificity.

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Dr Walsh reports having no financial or advisory relationships with corporate organizations related to this activity.
Off-Label Product Discussion: The author of this article does not include information on offlabel use of products.
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A screening test is effective if early detection reduces cancer mortality and the number of false positives is acceptably low. Ideally, evidence about screening effectiveness comes from randomized clinical trials. Randomized clinical trial data are available for mammography for breast cancer, chest radiography and sputum cytology for lung cancer, and fecal occult blood testing (FOBT) for colon cancer. Well-designed case-control studies (such as those done for sigmoidoscopy) also provide evidence that screening tests are effective.

Some screening test evidence is indirect and concerns test accuracy and the prognosis of those screened. This indirect evidence may overestimate the value of screening tests because of several inherent biases: (1) lead time bias: earlier detection appears to prolong survival by increasing the interval between diagnosis and death; (2) length time bias: initial screening tends to find slower growing cancers with a better prognosis; and (3) overdiagnosis: screening may find abnormalities (like carcinoma in situ) that would regress or never become clinically apparent.

CURRENT CONTROVERSIDY TYPE OF CANCER

Although several cancer screening strategies are clearly established, new controversies arise regularly regarding what physicians should be doing to screen their patients for cancer. Current controversies include the following:

• Colorectal cancer — What screening tests should be used? How often should testing occur?
• Cervical cancer — At what age can screening be discontinued? Is there a role for human papillomavirus (HPV) typing?
• Breast cancer — Should mammography be performed? Is mammography screening useful for women in their 40s and those older than 70 years of age?
• Ovarian cancer — Is screening useful?
• Lung cancer — Does screening reduce mortality? What is the role of screening with spiral computed tomography (CT)?
• How should we make decisions about screening for cancer in the elderly?

Table 1. Selected Guidelines for Colon Cancer Screening*

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>US Preventive Services Task Force</td>
<td>The benefits of screening substantially outweigh potential risks. The quality of evidence, magnitude of benefit, and potential risks vary with each method.</td>
</tr>
<tr>
<td>American College of Gastroenterology</td>
<td>Colonoscopy every 10 years is preferred when available. An alternative strategy is annual FOBT plus flexible sigmoidoscopy every 5 years.</td>
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<tr>
<td>American Cancer Society</td>
<td>Annual FOBT plus flexible sigmoidoscopy every 5 years is recommended. Alternative strategies are annual FOBT, sigmoidoscopy every 5 years, colonoscopy every 10 years, or double-contrast barium enema every 5 years.</td>
</tr>
<tr>
<td>Multidisciplinary Expert Panel of the Agency for Health Care Policy and Research</td>
<td>There is strong evidence for annual FOBT or flexible sigmoidoscopy every 5 years. On a theoretical basis, not as a result of research findings, the combination of annual FOBT plus sigmoidoscopy every 5 years is recommended. There is a strong rationale but no direct evidence for a double-contrast barium enema study every 5 to 10 years, or colonoscopy every 10 years.</td>
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* These guidelines refer to asymptomatic, average-risk adults aged 50 years or older.

Data from US Preventive Services Task Force; Rex et al; Smith et al; W inawer et al.

Colon Cancer

Colon cancer has a high incidence (it is the second most common form of cancer in the United States), as well as a high mortality rate. Several randomized clinical trials of FOBT and case-control studies of flexible sigmoidoscopy have shown that mortality from colon cancer is reduced by using either screening method.

Which Test and How Often? The US Preventive Services Task Force (USPSTF), an evidence-based organization, recommends, as do many professional societies, that all persons aged 50 years and older be screened for colon cancer (Table 1). The USPSTF does not recommend a particular screening strategy because no current evidence conclusively shows the superiority of a single test over others. The quality of the available tests and the evidence for their effectiveness must be weighed against the potential risks of each method.

US television news reporter Katie Couric is a vocal advocate of colon cancer screening because her husband died from the disease. Because Ms Couric's husband was only 42 years of age at the time of his death, some patients and physicians are asking whether screening for colon cancer should be initiated in patients younger than 50 years of age. In a recent employer-based colonoscopy screening program involving 906 volunteers aged 40 to 49 years, no cancers were detected, and any type of neoplasia was rare. The researchers estimated that 250 to 1000 individuals had to be
screened to detect 1 case of neoplasia. In many of these patients, the neoplasias were within reach of a sigmoidoscope. The finding that colon cancer and neoplasia were rare in this population supports the recommendation that screening begin at the age of 50 years.

Is colonoscopy more effective compared with other screening tests? An important criterion for cancer screening is whether the screening test reduces cancer-specific mortality. Two recent observational studies of patients undergoing colonoscopy had predictable results — colonoscopy showed some lesions that would not have been detected using sigmoidoscopy alone. These studies were not designed to determine the risk of proximal advanced neoplasia in patients with or without distal neoplasia but rather to assess morbidity and mortality. The results of these studies showed that distal polyps predicted proximal neoplasia, but some patients with proximal neoplasia did not have distal polyps. If sigmoidoscopy alone had been used, and if every adenomatous polyp had triggered colonoscopy, more than 80% of proximal lesions would have been detected.

To assess the impact of adding FOBT to sigmoidoscopy, a U.S. Veterans Affairs (VA) study assessed the use of 1-time FOBT in addition to sigmoidoscopy. More lesions were detected when using both tests than when using sigmoidoscopy alone, but again some lesions were not detected. Important limitations of this study were that only 1-time, rather than annual, FOBT was assessed; no assessment of morbidity and mortality was performed; and the study population was markedly different from the general population (97% were men; 14% had a family history of colon cancer).

Although colonoscopy has not been evaluated in a randomized clinical trial, it was an integral part of the FOBT trials, which showed a reduction in mortality with screening. Although the rationale for using colonoscopy to reduce mortality is strong, the evidence is indirect. Because more risks (eg, perforation) are associated with colonoscopy compared with other screening methods, the risk-benefit ratio must be considered when determining which patients should undergo routine screening.

**Virtual Colonoscopy.** One of 2 newer options, virtual colonoscopy is a noninvasive test in which thin-section CT is used to examine the inside of the colon. The largest study to date, involving 300 participants, was conducted at the VA Medical Center in San Francisco. The researchers found that virtual colonoscopy was 100% sensitive for cancer and 90% sensitive for polyps larger than 1 cm. The procedure was not as successful at detecting smaller polyps (sensitivity, 59% to 80%); however, smaller polyps are less likely to be clinically important.

Is virtual colonoscopy easier to perform or more effective than colonoscopy? This method also requires bowel preparation and insufflation, and it is unclear whether it will be more acceptable than colonoscopy. Test interpretation is time consuming, because the radiologist must evaluate the images in multiple dimensions to detect abnormalities. Even if virtual colonoscopy were 100% sensitive and 100% specific, it would need to be less than one half the cost of colonoscopy, and compliance would need to be 15% to 20% better before it could replace colonoscopy. No data are available regarding the effects of virtual colonoscopy on morbidity and mortality.

**Fecal DNA Testing.** The second newer option, fecal DNA testing, can detect mutations of the adenomatous polyposis coli (APC) tumor suppressor gene along the entire length of the colon. A potential advantage of this method compared with FOBT is that patients need no advance preparation, such as changing diet or discontinuing nonsteroidal anti-inflammatory drug therapy. In a small study, fecal DNA testing detected APC mutations in 26 of 46 patients with known colon cancer or polyps and detected none in 28 control patients. The test was 91% sensitive for colorectal cancer, 73% sensitive for polyps, and 100% specific.

Studies comparing fecal DNA testing with FOBT and colonoscopy are under way. Ultimately, mutations in other genes associated with colon cancer, such as K-ras and p53, will also need to be detected. Virtual colonoscopy and fecal DNA testing may have a future role in cancer screening but are not yet ready for routine use.

Any screening for colon cancer is better than no screening. In 1999, only 21% of individuals had undergone FOBT in the preceding year, and only 34% of individuals had undergone sigmoidoscopy or colonoscopy in the preceding 5 years. The focus should be on increasing patient awareness of colon cancer screening and ensuring that all individuals aged 50 years and older undergo screening, rather than on which test is superior.

**Cervical Cancer.**

The biggest success story in the history of cancer screening is the Papanicolaou (Pap) smear. Cervical cancer mortality has decreased by 70% over the past 50 years, largely due to Pap-smear screening. Once the number-one cause of cancer deaths among US women, cervical cancer now ranks 13th.
Because the time required for initial abnormalities to develop into cervical cancer is approximately 10 years, there are multiple opportunities for detection, even if screening is performed less frequently than the 1-year interval now popularly used. The USPSTF recommends initiating Pap smears within 3 years of the onset of sexual activity or at 21 years of age and repeating screening at least every 3 years until the age of 65 years for women who have had consistently normal smears and who are not at high risk. Most organizations do not address the upper age-limit at which screening can be discontinued. However, the American Cancer Society (ACS) recently published new recommendations, which state that women aged 70 years and older may discontinue screening for cervical cancer if they have had 3 or more consecutive normal tests and no abnormal results in the past 10 years.

The only major risk associated with cervical cancer screening is that the patient may have to undergo additional procedures after abnormal test results, only to find that the patient does not have cervical cancer. Another risk is that the screening identifies cancers that may not have become clinically apparent. Many early lesions, many low-grade lesions, and some high-grade lesions will regress without treatment. It is unclear, therefore, how aggressively patients should be screened. It is also important for the physician not to underestimate the worry and anxiety women may experience when notified of abnormal results of a Pap smear.

Discontinuing Screening. The risks of high-grade cervical lesions and cancer decline with increasing age, and a history of normal Pap tests further reduces risk. Thus, the utility of continuing to screen previously screened women is unclear.

Using data from the Heart and Estrogen/Progestin Replacement Study (HERS), which evaluated hormone replacement therapy for secondary prevention of coronary heart disease (CHD), Sawaya and colleagues examined the predictive value of an abnormal Pap smear for cervical cancer in older women. In the HERS study, 2763 postmenopausal women with CHD, all of whom had an intact uterus, received estrogen plus progestin or placebo and had annual Pap smears. The 2561 women with normal baseline Pap smears were included in the secondary analysis. Subsequent abnormal Pap smears were classified as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (SIL), high-grade SIL, or atypical glandular cells of undetermined significance (AGCUS).

Of the 2561 women analyzed, the average age was 66.7 years; 89% of the women were white; and 60% had 12 or fewer years of education. Seventy-eight women (3%) had an abnormal Pap smear 1 year after baseline, and 32 women (1.4%) had an abnormal Pap smear 2 years after baseline. The incidence of new cytologic abnormalities was 23 per 1000 person-years; the majority of abnormalities were ASCUS (67.3%) or AGCUS (21%).

These 110 abnormal Pap smears prompted 231 additional interventions. Most of these interventions (n = 112) were repeated Pap smears; however, others included 33 colposcopies, 30 cervical or vaginal biopsies, 35 endocervical curettage procedures, 8 endometrial biopsies, 4 dilation and curettage procedures, and 9 cone biopsies or loop electrocautery excision procedures. At the end of

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<tr>
<td>US Preventive Services Task Force</td>
<td>Indirect evidence suggests beginning screening within 3 years of onset of sexual activity or age 21 years, whichever occurs first, then rescreening at least every 3 years. Women &gt;65 years need not be routinely screened if they have had adequate recent screening with normal Pap test results, and are not otherwise at high risk for cervical cancer.</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists</td>
<td>Pap testing should be conducted annually for all women who have been sexually active, regardless of age, and all women who have reached age 18 years. After 3 or more normal Papanicolaou (Pap) test results, less frequent screening may be offered to low-risk patients.</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>Screening should begin about 3 years after the start of vaginal intercourse, but no later than age 21 years, with a regular Pap test annually or a liquid-based Pap test every 2 years. Average-risk women ≥30 years of age who have had 3 consecutive, normal results may be screened every 2 or 3 years. Women aged ≥70 years may stop being screened if they have had 3 or more consecutive, normal results and have had no abnormal results in the past 10 years.</td>
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Data from US Preventive Services Task Force; American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice; Saslow et al.
the 2-year follow-up period, 103 women had a known final diagnosis. Ninety-four received a “normal” diagnosis, which was assigned only if 2 other Pap smears within the 2-year follow-up period were normal and/or if colposcopy was normal. Six women had low-grade histologic conditions (HPV infection or grade I cervical intraepithelial neoplasia [CIN]), 2 had high-grade histologic conditions (grade I CIN or grade II vaginal intraepithelial neoplasia), and 1 had endometrial hyperplasia without atypia. Most importantly, there was no grade II or grade III CIN or invasive cancer.

The researchers concluded that in previously well-screened postmenopausal women, cervical abnormalities are rare, and that the positive predictive value of screening (the percentage of abnormal tests that truly indicate disease) is low. Among women with any cervical abnormality, the positive predictive value of screening in identifying a high-grade cervical histologic condition within 1 year was 0%. Within 2 years, it was 0.9%; thus, 99.1% of abnormalities were not high-grade histologic conditions. A positive finding in a previously screened postmenopausal woman is more likely to be a false positive than a true positive.

One important caveat concerning the analysis by Sawaya et al is that the women in the HERS study were generally at low risk for cervical cancer. These results cannot be generalized to women who are at higher risk, such as those who have never been screened, those who have a history of abnormal Pap smears, or those who have a new partner. Nevertheless, the results support the idea that screening can be discontinued in postmenopausal women who have had a normal Pap smear for 2 previous years. These results also indirectly support the recommendation of the USPSTF that screening can be discontinued after 65 years of age if the patient has been previously well-screened and is not at high risk for cervical cancer.

After Hysterectomy. Two critical factors must be considered when making a decision regarding the need for cervical cancer screening after hysterectomy: whether the woman has a cervix, and whether the hysterectomy was performed because of cervical cancer. In women who have undergone supra-cervical hysterectomy, the cervix remains. If a woman does not know which procedure was performed, an examination may be needed to determine whether the cervix is present. If a woman has had her entire uterus removed, then any screening would be for vaginal cancer. Although vaginal cancer is rare, the risk factors are the same as those for cervical cancer. Thus, screening women with a history of cervical cancer may be reasonable.

Same-Sex Partner or No Sexual Partners. The main causative agent of cervical cancer is HPV; it is unknown whether a woman can develop cervical cancer without HPV exposure. Many women who currently have a female sex partner may have previously had 1 or more male sex partners. Thus, the potential for HPV exposure exists. HPV exposure may occur from a female partner, although the risk of HPV reaching the cervix is lower than with exposure from a male partner. Screening at less frequent intervals is probably reasonable in women with female sex partners.

In women who have never had intercourse, the risk of cervical cancer is low; however, it is unclear whether the risk is zero. The utility of Pap-smear screening in women who have never been sexually active is not known, but a 1-time or infrequent Pap smear may be reasonable.

HPV Typing. High-risk HPV types have been documented (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The US Food and Drug Administration recently approved the use of HPV typing in combination with Pap smears for use in cervical cancer screening. The ACS suggests it may be reasonable to perform combination testing in women aged 30 years and older. The potential utility of combination testing is that, in a woman who is negative for HPV, screening could be deferred for 3 years. It is unclear how testing should proceed for women who are positive for HPV but negative for cervical cytology. Guidelines for management of this scenario need to be developed.

HPV typing is not recommended for routine cervical cancer screening. However, HPV typing can be useful in the triage of an abnormal Pap smear (ASCUS) to help determine whether the patient needs immediate colposcopy or repeated testing.

Breast Cancer

Breast cancer is the most commonly detected nonskin malignancy in U.S. women and the second leading cause of death from cancer. The newest debate about breast cancer is whether mammography screening reduces mortality and, by extension, whether it should be performed. Additional questions remain about screening women in their 40s and screening older women.

In a recently published meta-analysis conducted by the Cochrane Collaboration, researchers concluded that mammography screening does not reduce mortality. Olsen and Gøtzsche reviewed reports on 8 mammography screening trials and assigned a quality score to each study based on whether women were adequately randomized, whether postrandomization exclusions were few
and unbiased, and whether there were reliable data on outcomes. A study was ranked "high quality" if all criteria were fulfilled, "moderate quality" if some minor protocol violations occurred, "poor quality" if major violations occurred, and "flawed" if major violations occurred and the investigators could document important bias. The investigators then assessed a variety of outcome measures: overall mortality, breast cancer mortality, all cancer mortality, use of surgery, use of adjuvant therapy, and adverse effects. They analyzed the results for each quality-ranked group separately.

Olsen and Götzsche identified zero high-quality studies, 3 moderate-quality studies, 3 poor-quality studies, and 2 flawed studies. The moderate-quality studies showed no effect of screening on breast cancer mortality after 7 or 13 years of follow-up (relative risk [RR], 1.05; 95% confidence interval [CI], 0.83–1.33). Only the poor-quality studies showed an effect on breast cancer mortality (RR, 0.68; 95% CI, 0.58–0.78).

Because each quality-ranked group was evaluated separately, and because several well-established screening trials were excluded when the investigators found some evidence of bias, the summary showed that screening afforded no reduction in breast cancer mortality. This is true of screening for many other cancers, because cancer from any cause is usually a small proportion of overall deaths, and it had no effect on mortality from other cancers. More mastectomies were performed in the screened group.

The investigators concluded that breast cancer mortality is an unreliable outcome measure and is biased in favor of screening. They argued that inconclusive evidence exists regarding whether mammography screening reduces mortality, and that screening leads to more aggressive treatment. The authors reached this conclusion even though point estimates in 6 of the 8 studies showed a reduction in breast cancer mortality with screening after 13 years.

If a trial is flawed, should the results be rejected? Or should the flaw simply be taken into consideration when interpreting the results? USPSTF authors recently analyzed many of the same trials as those considered in the Cochrane meta-analysis. These authors acknowledged some of the flaws but did not reject the results of the flawed trial. They therefore reached somewhat different conclusions. The USPSTF now recommends that women aged 40 years and older be screened with mammography every 1 to 2 years. They also acknowledge that the data are less clear for women in their 40s and for those aged 70 years and older, compared with the data for women in their 50s and 60s (Table 3).

**Women in Their 40s** Randomized controlled trials of mammography screening have not demonstrated a reduction in mortality in women in this age group, which fuels the controversy regarding whether screening for breast cancer in women in their 40s is justifiable. The major risk factor for breast cancer is increased age; therefore, a positive result on a mammogram for a woman in her 40s is more likely to be a false positive than a true positive. For women in their 40s who have no family history of breast cancer, the positive predictive value of mammography screening is 4%, whereas for women in their 50s and 60s, the predictive value is 13%.

Because no conclusive evidence exists for routinely recommending a mammogram for women in their 40s, a shared decision-making approach is appropriate. This approach includes discussing the pros and cons of screening with the patient. Physicians should point out that mammography has a lower sensitivity in younger women, and, for that reason, leads to a higher incidence of false positives. Thus, mammography is a less informative screening test for patients in this age group. Other components of the decision-making process include assessing the patient’s other risk factors or protective factors.

**Table 3. Selected Guidelines for Breast Cancer Screening**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>US Preventive Services Task Force</td>
<td>Women aged ≥40 years should have mammography every 1 to 2 years. The evidence for reduction of mortality is strongest for women aged 50 to 69 years. The evidence is generalizable to women aged ≥70 years if their life expectancy is not compromised by comorbid disease. Most, but not all, studies indicate a lower mortality risk for women undergoing mammography at ages 40 to 49 years. Evidence is insufficient to recommend for or against routine clinical breast examination.</td>
</tr>
<tr>
<td>American College of Radiology</td>
<td>Asymptomatic women aged ≥40 years should have annual mammography. Monthly breast self-examination and annual clinical breast examination should also be performed, although the benefit of these periodic examinations is scientifically unproved. Mammography before age 40 years may benefit women who are at high risk for breast cancer.</td>
</tr>
<tr>
<td>American Cancer Society (an update is expected in 2003)</td>
<td>Annual mammography should begin at age 40 years. Cessation of annual screening is not age related but rather is a function of comorbidity. A clinical breast examination should be conducted shortly before or after the mammogram.</td>
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Data from Humphrey et al; Feig et al; Leitch et al.

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If women in their 40s decide to be screened, mammography should be performed annually rather than every 2 years. Although cancer in this age group is uncommon, it tends to be more aggressive. Screening at 2-year intervals may not be frequent enough to detect cancers that develop in the interim.

**Older Women.** Nearly one half (47%) of all cases of breast cancer in the United States are diagnosed in women older than age 65 years, and 52% of breast cancer mortality occurs in this age group. A major consideration when making decisions regarding continued screening is competing mortality. If a woman has end-stage congestive heart failure, for example, screening is less likely to improve life expectancy compared with screening in a healthy woman. Clinical trials have generally excluded older women; thus no evidence from clinical trials shows that screening reduces breast cancer mortality in this age group. However, women older than age 65 years who are screened are less likely to die from metastatic breast cancer. Metastatic breast cancer is a good surrogate for breast cancer mortality, because most women with metastatic breast cancer die from the disease.

Mammography screening is probably effective in older women, but the benefits of screening must be balanced against the potential risks and costs of detecting early lesions, which may have little impact on subsequent morbidity and mortality. Although the USPSTF endorses mammography screening for women aged 70 years and older, it cautions that mammography may not be beneficial if a woman's life expectancy is compromised by comorbid disease.

**Ovarian Cancer**

One major obstacle to effective screening for ovarian cancer is the rarity of the disease. For a woman with no family history of ovarian cancer, the lifetime risk is 1.2%. A woman with 1 affected relative has a risk of 5%; a woman with 2 affected relatives has a risk of 7%. If the rare hereditary syndrome is present in a woman's family, the risk of ovarian cancer is 40%.37

The risk factors for ovarian cancer include increased age; nulliparity; North American or Northern European descent; personal history of endometrial, colon, or breast cancer; and a family history of ovarian cancer.37 Use of fertility drugs may increase risk, but this has not been shown conclusively.38 Protective factors include more than 1 full-term pregnancy and breast feeding.37 Several studies have shown that women who take oral contraceptives have a 37% reduction in risk for ovarian cancer.37

A 1995 National Institutes of Health consensus conference found no evidence that ovarian cancer screening is beneficial. The group concluded that screening may cause some harm (eg, prompting women to have unnecessary surgery). Many organizations recommend routine pelvic examination to screen for ovarian cancer, but no evidence shows that pelvic examination is a good method for detecting the disease. If a woman has the hereditary syndrome or 2 or more relatives with ovarian cancer, referral to a gynecologic oncologist is reasonable. Many organizations recommend the serum CA-125 assay, rectovaginal pelvic examination, and transvaginal ultrasonography for women who are at high risk for ovarian cancer, but they acknowledge that it is not known whether screening reduces mortality.

In a randomized clinical trial of ovarian cancer screening, 22,000 volunteers in the United Kingdom underwent either annual CA-125 screening or no screening for 3 years.39 Women with an elevated CA-125 level underwent ultrasonography. If ultrasonography detected abnormalities, the women underwent surgery. Patients were followed up for 7 years.

In the intervention group, 468 women had elevated CA-125 levels. Of these, 29 eventually underwent surgical investigation. Only 6 of the 29 women had cancer. An additional 10 cases of cancer, undetected by screening, developed in the intervention group. Thus, a total of 16 patients in the intervention group had cancer, compared with 20 patients in the control group. The median survival of women with ovarian cancer was slightly longer in the intervention group (73 months) compared with the control group (42 months; P = .01). Quality of life was not evaluated, although it is likely that quality of life was reduced in patients undergoing therapy for ovarian cancer. There was no significant difference in mortality from ovarian cancer between the control group (n = 18) and the intervention group (n = 9; P = .083).

Overall, the screening protocol was reasonably sensitive and specific, and the positive predictive value was 20.7%. Because of the low prevalence of ovarian cancer, however, the utility of screening is limited. Thousands of women must be screened to detect only a few cases of cancer. No reduction in mortality has been shown.

**Ongoing Studies.** Two ongoing studies will further address the question of ovarian cancer screening. The Prostate, Lung, Colorectal, and Ovarian
Cancer (PLCO) trial, sponsored by the National Cancer Institute (NCI), involves 74,000 women and approximately the same number of men, aged 55 to 74 years, across the United States. In the ovarian cancer screening component, women undergo CA-125 screening at study entry and annually for 5 years. They also undergo transvaginal ultrasonography at baseline and annually for 3 years. The subjects will be followed up for 13 years. In an even larger study, the United Kingdom Trial of Ovarian Cancer Screening, 200,000 women will undergo multimodal screening and be followed up for 7 years.

LPA Assay. A serum assay for another tumor marker, lysophosphatidic acid (LPA), may show some promise as a screening tool. Preliminary studies have shown that LPA is elevated in 90% of women with stage I ovarian cancer and in 100% of those with stage II to IV cancers. The use of LPA must be evaluated in screening studies on a larger scale.

Lung Cancer

Lung cancer is the leading cause of cancer mortality in both men and women, but several studies in the 1970s and 1980s concluded that screening with chest radiographs and/or sputum cytology did not reduce mortality. Twenty-year follow-up data from one major trial, the Mayo Lung Project, show that more early-stage lung cancers were detected in the screened group, and survival was slightly longer, but that screening had no effect on mortality.

The effect of lung cancer screening on mortality was recently explored in a systematic Cochrane review of 7 studies. The authors found that frequent chest radiographs were associated with an increase in mortality (RR, 1.11; 95% CI, 1.00–1.23). The addition of sputum cytology to chest radiographs had no significant effect on outcome. Thus, current evidence does not support screening with either chest radiography or sputum cytology, and frequent screening may be harmful. Only 1 of the studies reviewed included women, thereby limiting the ability to generalize the results.

Spiral CT. Spiral CT is the newest screening option proposed for lung cancer. The Early Lung Cancer Action Project published baseline data in 1999. In this trial, 1,000 high-risk men were screened with CT. The investigators detected 27 cases of cancer (85% stage I) but also detected a large number of incidental nodules requiring further evaluation. Because these were baseline findings, no information is available regarding mortality.

Spiral CT may detect lesions that would soon become clinically apparent. The potential also exists for overdiagnosis of lesions that may not become clinically apparent. It is unknown whether the benefits of spiral CT outweigh the risks, given the large number of incidental nodules that require evaluation. Spiral CT is not currently recommended for routine use in clinical practice.

The NCI is sponsoring the Lung Cancer Screening Study, in which high-risk individuals are being screened by either CT or chest radiography; results will be available in 2005. No current evidence shows that lung cancer screening reduces mortality. However, one intervention can dramatically reduce lung cancer risk — all smokers should be encouraged by every available means to quit smoking.

Cancer Screening in the Elderly

Cancer screening in the elderly is complex; therefore, many questions remain unanswered. Incidence and mortality rates for most cancers (except for cervical cancer) are higher in the elderly, and hence, more cases will be found with screening. A major factor affecting the decision to screen is the impact of competing morbidity and mortality from other diseases. If a woman has end-stage congestive heart failure, then mammography screening may not be warranted, since her risk of death from breast cancer is very low compared with her risk of death from heart disease.

The incidence of colon cancer increases with age; therefore, the elderly are at high risk for colon cancer. Although randomized controlled trials have typically not included men and women over the age of 74 years, the higher incidence of colon cancer in that age group increases the likelihood that fewer individuals would need to be screened in order to detect a case. Elderly women who undergo mammography have a lower risk of death from metastatic breast cancer, so screening is effective in these women. Pap-smear screening is an exception. Elderly women are at extremely low risk for cervical cancer. Hence, discontinuing screening of elderly women with a history of adequate smears is warranted. For ovarian and lung cancer, there is no evidence that screening reduces mortality in any age group.

Age alone should not be the basis of decisions about cancer screening in the elderly. The decision-making process should be individualized and should consider competing morbidity and mortality, the patient’s functional status, and the likelihood that an abnormality detected with screening will significantly change the patient’s life. A framework for individualized decision making has been proposed that includes the following considera-
tions: (1) risk of death from cancers that are detectable by screening, including life expectancy of the individual and the age-specific mortality rate of the cancer; (2) potential benefits (eg, the decreased likelihood of false-positive or false-negative results, and the fact that fewer individuals need to be screened in order to prevent 1 death from cancer); (3) the potential risks of cancer screening (eg, complications from diagnostic procedures, psychological stress and anxiety, and detection of indolent cancers); and (4) the patient’s individual values and preferences (eg, the patient’s desire to be involved in the screening decision, and his or her view of the potential benefits and risks). This framework can be useful in helping the patient to make informed decisions.

Summary of Recommendations for All Cancers and All Age Groups

• All men and women aged 50 years and older should undergo colon cancer screening: annual FOB T plus flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, or double-contrast barium enema every 5 years.

• Screening for cervical cancer with Pap smears should begin within 3 years of the onset of sexual activity and should be repeated at least every 3 years. Screening can usually be discontinued after the age of 65 or 70 years.

• HPV typing may be useful for triaging abnormal Pap smears, but it is not currently recommended for routine screening.

• Although the utility of mammography continues to be debated, current screening practices should not change. Women aged 50 to 69 years should undergo mammography every 1 to 2 years. Physicians should discuss the pros and cons of mammography screening with women aged 40 to 49 years and those aged 70 years and older.

• Screening for ovarian cancer is not recommended in women who are at average risk for the disease but may be considered in women who are at high risk. Women at high risk should consider taking oral contraceptives.

• No evidence shows that screening for lung cancer reduces mortality.

• Decision making about cancer screening in the elderly is complex. The physician and patient together should consider the risk of death from cancers that are detectable by screening, the potential benefits and risks of screening, and the patient’s individual values and preferences.

REFERENCES


