Adult Preventive Health Care: Cancer Screening

Population: Adults, 18 years and older

Objectives: Implement an evidenced-based strategy for cancer screening in adults.

Key Points

Breast Cancer Screening

Modality. Mammogram. Evidence is insufficient to recommend for or against clinical breast exam and breast self examination.

Initiate. Average risk. Recommend screening mammography for women age 40 and older. Evidence for mortality reduction is strongest for women aged 50 and older [A]. Evidence is weaker and absolute benefit of mammography is smaller for women age 40-49.

High risk. Women at increased risk of breast cancer (see Table 1) may benefit from earlier screening and discussion of risk reduction strategies[D].

Frequency. Little evidence is available regarding frequency of screening. Most experts recommend mammography either annually or every 1-2 years [D].

Terminate. Consider screening depending on life expectancy (even for women over 69) [D].

Cervical Cancer Screening

Modality. Papanicolaou (Pap) smear of cervical cells or liquid based cervical cytology (ThinPrep®).

Initiate. Start within 3 years after onset of vaginal intercourse [B] or at age 21 for women who are not sexually active [D]. Women who have undergone a total hysterectomy do not require screening unless the hysterectomy was performed because of cervical cancer or its precursors [C].

Frequency. Low risk. Annually with conventional Pap smears or every two years using the ThinPrep until age 30. Starting at age 30, women who have had three consecutive technically satisfactory normal or negative cytology results may be screened every two to three years [C]. (see text for details)

High risk. Screen annually [D].

Terminate. Screening may be discontinued in women past age 65 (USPSTF) or age 70 (ACS, NCCN) who have at least three normal or negative smears in the past 10 years and no previous history of cervical abnormality [C].

Colon Cancer Screening

Modality. Recommended methods include: fecal occult-blood testing, flexible sigmoidoscopy, or colonoscopy. (Digital rectal exam is not effective in screening for colorectal cancer.)

Initiate. For average risk, asymptomatic patients, screening should begin at age 50.

Frequency. Average risk. Fecal occult-blood testing (FOBT): annually [A]. Flexible sigmoidoscopy (FS): every 5 years [A]. FOBT/FS: annually/every 5 years [B]. Colonoscopy: every 10 years [B]. Air or double-contrast barium enema (acceptable modality, but not recommended): every 5 years [B]. The frequency of screening has not been adequately evaluated in clinical trials.

High risk. Patients at increased risk of colorectal cancer should undergo more aggressive screening; details of screening vary based upon the nature of the increased risk – see Table 4.

Terminate. No definite age cutoff exists for discontinuing screening.

Prostate Cancer Screening

Modality. Prostate-specific antigen (PSA) and digital rectal examination. Both have specificity limitations.

Initiate. Clinicians who screen for prostate cancer should share decision making with patients [A], giving objective information about the potential risks and benefits of screening.

Average risk. For men > age 50, consider initiating PSA screen.

High-risk. For men with positive family history and for African Americans, consider starting PSA screening at age 40 [D].

Frequency. Annually.

Terminate. Stop when life expectancy is less than 10-15 years [C].

Note: Appendix A graphically presents cancer screening intervals by patient age.

* Levels of evidence reflect the best available literature in support of an intervention or test:
A= randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel
Clinical Background

Breast Cancer Screening

Clinical Background

Burden of Suffering

Breast cancer is the most common non-cutaneous cancer in American women. An estimated 192,200 new cases were diagnosed in 2001 with 40,600 deaths. 2003 estimates (ACS) are 211,300 new cases with 40,200 deaths. Breast cancer is surpassed only by lung cancer as the leading cause of cancer death in American women. Non-Hispanic white women have the highest incidence rate of breast cancer; however African American women have the highest case fatality rates.

The number of reported cases of breast cancer has increased 36% in the past 20 years. This may be due to both increased screening with mammography and a true increase in disease incidence. There has been a dramatic increase (750%) in the number of ductal carcinoma in situ (DCIS) detected in the past two decades. Since it is not yet possible to predict which DCIS will progress to invasive breast cancer, all DCIS tumors are currently treated with mastectomy or some combination of lumpectomy, radiation, and tamoxifen.

Mortality rates declined by 1.4% per year from 1989-1995 and by 3.2% afterwards. This reduction is probably a result of many factors, including early detection and treatment, especially the application of adjuvant systemic tamoxifen.

Rationale for Recommendations

The relative risk of breast cancer death among women of all ages randomized to screening in eight prospective randomized clinical trials was 0.84 (95% CI , 0.77-0.91).

Mammography in women age 50 to 69. From prospective randomized clinical trials, the evidence for screening is strongest in women age 50 to 69 with a relative risk of 0.76 in breast cancer mortality after 10 or more years of regular screening. The mortality benefit appears to emerge approximately 5 years after the initiation of screening. Regular screening of 10,000 50 year-old women for 10 years saves about 37 lives. This is the most beneficial and cost-effective age group to screen.

Mammography screening in women age 40 to 49. Evidence that screening mammography reduces mortality from breast cancer in this age group is weaker. The apparently lower benefit in younger women may be due to a combination of factors. Breast cancer incidence in younger women is much lower than in women in their 50s and 60's, and mammography is less accurate.

Based on the incidence rates and effectiveness of screening, if 10,000 40 year-old women were screened every year for 10 years, about 4 lives would be saved as compared to 37 lives if screening started at age 50. However, women in their 40’s have more years of life saved than older women.

A meta-analysis of six randomized controlled trials of mammography in women age 40 to 49 indicates a relative risk reduction in breast cancer mortality of 15% after 13 years of annual screening. A reduction in breast cancer mortality was not observed until approximately 10 years after the onset of screening and many women enrolled were over 45 years old at the time of study entry. Therefore, some of the observed reduction in mortality may have been due to cases detected in women as they entered their early to mid 50s.

Younger women are much more likely to have false negative results as the sensitivity of screening mammography is lower in pre-menopausal women who have dense, nodular breasts. As women age, breast tissue becomes more fatty and breast cancers are more easily detected by screening mammography.

Younger women are also more likely to have false positive mammogram results. False positive results necessitate further evaluation and have been shown to increase anxiety. An observational cohort study over a 10 year period of women age 40-69 enrolled in a community-based HMO in Boston found that 23% of women tested had at least one false positive screening mammogram. The median number of screening mammograms over the 10 year period was 4. About 97% of women aged 40-49 who have abnormal mammograms do not have cancer, compared to 86% of women age 50 and older.

Mammography screening in women over age 69. Women aged 70 and older face a higher absolute risk of breast cancer. However, due to the small number of women over age 69 enrolled in randomized controlled trials, there are insufficient data on the effectiveness of mammography in older women. Women over age 69 have been shown to benefit from screening by detection of earlier stage lesions in the screened population. However, cost effectiveness may decrease by age 75 to 80 due to lower life expectancy. The decision to screen in this age group should be based on the woman’s general health and consideration of co-morbidities that may severely limit the woman’s life expectancy.

Frequency of mammography screening. Screening intervals ranged between 12 and 33 months in the randomized controlled trials on breast cancer screening. No definitive mammography screening interval has been determined, but many societies currently recommend annual screening. Individuals with specific breast conditions or risk profiles may require adjustments in this interval.

Clinical Breast Examination (CBE). There is insufficient evidence to recommend for or against CBE. There has been no screening trial comparing CBE (without...
mammography) to no screening. The sensitivity of clinical breast exam (CBE) ranges 40-69%, specificity 86-99% and positive predictive value from 4-50%, using mammography and interval cancer as the criterion standard.

Up to 25% of the palpable breast cancers found on clinical breast exam (CBE) are not visible on mammography and warrant further evaluation with ultrasound and/or breast biopsy. However, only 4% of woman with abnormal CBE are subsequently diagnosed with cancer. Clinical breast examination may augment mammography, but cannot be used alone as a screening tool.

Breast Self-Examination. There is no randomized controlled trial in American women on the efficacy of breast self-examination (BSE). A large Chinese and a Russian randomized controlled trial on BSE revealed no decrease in mortality from breast cancer and a lack of stage shift. A substantial increase in the number of benign breast lesions were detected in women randomized to BSE.

Special Considerations: Risk Factors (Table 1)

Aging is the major risk factor for breast cancer. Women with a personal history of breast cancer are at increased risk for a second primary breast cancer. Additional risk factors include a family history of breast cancer in a mother and/or sister, proliferative benign breast disease, particularly atypical hyperplasia, radiologically dense breasts, early age at menarche or late menopause, nulliparity and first child after age 30.

Women who received chest irradiation for conditions such as Hodgkin’s disease at age 30 or younger are at particularly high risk for breast cancer. Likewise, alterations in BRCA1 and BRCA2 genes make women substantially more susceptible to breast cancer than women with wildtype genotypes. Consider referral to a breast specialist to start earlier screening and discussion of risk reduction strategies.

Radiation-Induced Breast Cancer. It is estimated that annual mammography of 100,000 women for 10 consecutive years beginning at age 40 would result in up to 8 radiation-induced breast cancer deaths.

Hormone Replacement Therapy (HRT). The Women’s Health Initiative study revealed a relative risk of 1.26 (CI 1.00-1.59) of invasive breast cancer with combined estrogen and progesterone therapy. The increase in diagnosis of breast cancer appeared after four years of use. In woman taking combined HRT, there were 8 additional new cases of breast cancer (38 versus 30) per 10,000 women per year.

The sensitivity of mammography is lower among women taking HRT. Retrospective cohort studies also indicate the use of HRT is associated with a decrease in mammographic specificity; the relative risk of a false-positive mammogram in women currently using HRT was 1.71 (CI 1.37-2.14). Short-term cessation of HRT may improve mammographic specificity and sensitivity, however there is a theoretical possibility that withdrawal of hormone may lead to false negative mammograms by shrinkage of tumors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence of Risk Factor</th>
<th>Risk</th>
<th>Comparison</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche</td>
<td>16%</td>
<td>&lt; 12 years</td>
<td>16 years</td>
<td>1.3</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>6%</td>
<td>&gt; 55 years</td>
<td>45-54 years</td>
<td>1.5</td>
</tr>
<tr>
<td>Age 1\textsuperscript{st} child born</td>
<td>21%</td>
<td>Nulliparous or &gt; 30 years</td>
<td>&lt; 20 years</td>
<td>1.9</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>15%</td>
<td>Any benign disease</td>
<td>No biopsy or fine-needle aspiration</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4%</td>
<td>Proliferative disease</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td>Atypical hyperplasia</td>
<td>4.0</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>8%</td>
<td>One first-degree relative affected</td>
<td>No first-degree relative affected</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two first-degree relatives affected</td>
<td>No first-degree relative affected</td>
<td>5.0</td>
</tr>
<tr>
<td>Combined HRT</td>
<td>Use &gt; 4 years</td>
<td></td>
<td>Never used</td>
<td>1.2</td>
</tr>
<tr>
<td>Chest Irradiation (*see text)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cervical Cancer Screening

Clinical Background

Burden of Suffering

In 2002, an estimated 13,600 cases of invasive cervical cancer were expected to occur, with about 4,100 women dying from this disease. Cervical cancer is more common among women of lower socioeconomic status and those with a history of multiple sexual partners, early onset of sexual intercourse (before age 17), infection with sexually transmitted disease (including human immunodeficiency virus [HIV]), smoking, or immunosuppression. Some experts believe that women whose male sexual partners have a history of either unprotected sex with multiple partners or with a partner who had a history of cervical cancer are also at increased risk.

Rationale for Recommendation

When to initiate screening. Many organizations recommend beginning screening within 3 years after onset of vaginal intercourse or at age 21, since many women in the United States begin intercourse by this age. There is no direct evidence supporting this recommendation, and screening women at this age will have a lower yield than in older women. It has been estimated that the incidence of invasive cervical cancer in women under age 25 is between one and three per 100,000 pap smears. Some experts believe that more frequent screening will allow detection of cervical dysplasia at an earlier stage and allow more conservative management, thus preserving reproductive potential. Women who have never engaged in sexual intercourse are not at risk of developing cervical cancer and thus do not need screening.

It is important that women who may not need a cervical cytology test obtain appropriate preventive health care, including contraception and prevention counseling, and screening and treatment of sexually transmitted diseases.

When to discontinue screening. Many women older than age 65 have never been screened or been screened fewer than two times for cervical cancer and these women would most likely benefit from continued screening efforts. More than one-quarter of all invasive cervical cancers occur in women older than 65, and almost half of all women who die from cervical cancer are over age 65. However, in women who have previously undergone routine screening (i.e., three or more technically satisfactory normal or negative cervical cytology tests without any abnormal or positive cytology tests within the past 10 years), the risk of dying from invasive cervical cancer is less than 0.2% at age 65 and less than 0.1% at age 74, thus the United States Preventive Services Task Force recommends that women age 65 or older may not need continued screening. The National Comprehensive Cancer Network and the American Cancer Society agree that women may elect to cease cervical cancer screening if they meet these criteria and are age 70 or older. There are no specific data to support one threshold over the other.

Women who have an intact cervix, a history of cervical cancer, in utero exposure to diethylstilbesterol (DES), and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as are in reasonably good health and do not have a life-limiting chronic condition.

Screening tests. The primary screening tests for cervical cancer are the Papanicolaou (Pap) smear of cervical cells or a liquid-based collection system (e.g., ThinPrep®). In 2003, approximately 8% of cervical screening tests at the University of Michigan were done with the Pap smear and 92% with the ThinPrep system. In ThinPrep, samples are collected from the cervix in the same manner as for a Pap smear, but the collection devices are rinsed into a buffered solution, transported to the laboratory and the slide is automatically prepared. This system collects more cells and leads to better quality slides. The accuracy of the Pap smear is improved if cervical samples of the transformation zone are collected with both an extended tip wooden or plastic spatula, and an endocervical brush rather than a cotton swab. However, the ThinPrep system is more sensitive (76% vs. 68%) and specific (86% vs. 79%) than Pap smear.

How often should screening be done. Screening intervals will vary depending on the cytologic method used. After women have undergone an initial conventional cervical cancer screening with a Pap smear, the procedure should be performed annually until age 30. If the initial screening test was based on the ThinPrep system, the procedure should be performed at least every two years until age 30. At age 30 or older, a physician and patient may elect to reduce the frequency of screening to every 2 to 3 years if the woman is low-risk (e.g., does not have a history of in utero exposure to DES, is not immunocompromised or HIV+) and has had three consecutive normal or negative cytology results.

New screening technology. The United States Food and Drug Administration (FDA) has approved a computerized device (AutoPap 300) as an adjunct to manual screening. The system is used to rescreen negative smears and approximately 10% to 20% of slides are classified as abnormal using a computerized cellular analysis. These slides are then reviewed by a pathologist.

HPV Testing. While routine testing on all patients for human papilloma virus (HPV) has been proposed as an alternative screening test the high prevalence of HPV in young women and low positive predictive value for higher-grade lesions limits its usefulness. At the University of Michigan, HPV testing for high risk subtypes are currently performed on the ThinPrep samples from patients with an ASCUS pap smear (indicated by checking the box on the requisition form). Patients > age 20 years old and positive for high risk HPV subtypes should be referred for colposcopy. HPV testing is not recommended in women ≤ 20 years old. For patients ≤ 20 years old and ASCUS or low grade abnormalities, repeat pap in 1 year. Adolescent patients are extremely unlikely to develop cervical
neoplasia and have a relatively high rate of clearing the virus. If repeat pap in 1 year is still abnormal, then patient should be referred for colposcopy. If negative for high risk HPV subtypes, the women may be followed with a repeat pap smear in one year, based on the negative predictive value, of our current HPV test, being 98%.

Role of a screening pelvic exam alone. The incidence and frequency of ovarian cancer in the general population is relatively low. Although ovarian tumors are occasionally detected on pelvic examination, they are usually at an advanced stage and associated with a poor prognosis. Screening for ovarian cancer with a CA 125 or ultrasound is not recommended for asymptomatic women. The predictive value of either test alone (less than 3 percent) yields an unacceptably high rate of false positive results. Currently no North American expert groups recommend routine screening for ovarian cancer.

Effectiveness of Screening. Correlational studies show significant declines in both the incidence of cervical cancer and cervical cancer mortality rates in North America and Western Europe following the introduction of screening programs. The reduction in mortality correlated closely with the intensity of the screening. Case control studies support the correlational data and show a decrease in the incidence of invasive cancer by 60-90%.

Increased frequency of screening is associated with a greater reduction in rate of cervical cancer (see Table 2). The yield from performing pap smears would also increase with less frequent screening; 33 cases of invasive cervical cancer would be identified per 100,000 women undergoing annual testing compared to 96 cases per 100,000 women undergoing screening every three years.

Table 2. Reduction in invasive cervical cancer rate in women* screened from age 35-64

<table>
<thead>
<tr>
<th>Screening intervals</th>
<th>Reduction in rate, %</th>
<th>Number of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>93.5</td>
<td>30</td>
</tr>
<tr>
<td>2 years</td>
<td>92.5</td>
<td>15</td>
</tr>
<tr>
<td>3 years</td>
<td>90.8</td>
<td>10</td>
</tr>
<tr>
<td>5 years</td>
<td>83.6</td>
<td>6</td>
</tr>
<tr>
<td>10 years</td>
<td>64.1</td>
<td>3</td>
</tr>
</tbody>
</table>

* Assuming 1 screen before age 35

Who gets screened. Although African-Americans and whites undergo screening at similar rates, Hispanics undergo screening at a lower rate than whites. Similarly, those who are less educated (i.e., less than a high school education) or have less income (e.g., less than the poverty level) are also at increased risk of not receiving a Pap smear. The elderly undergo screening at lower rates than younger women and there is an associated increase in the incidence of cervical cancer in the elderly.

Special Population

Total hysterectomy. Women who have undergone a total hysterectomy (with removal of the cervix) for benign gynecologic disease do not need to undergo screening with vaginal cytology. However, a health care provider should confirm and/or document via physical exam and review of the pathology report (when available) that the cervix was completely removed. Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines.

The NCCN recommends that women with a history of in utero exposure to DES, immunocompromised, HIV+ or cervical cancer should continue cervical cancer screening for as long as they are in good health and do not have a life-limiting chronic condition. It also recommends that women with a history of CIN II or III on biopsy or high-grade squamous intraepithelial lesions (HSIL) on cytology, or for whom one cannot document the absence of CIN II or III or HSIL prior to or as the indication for the hysterectomy, should be screened until there are three consecutive, technically satisfactory normal / negative cervical cytology tests, and no abnormal/positive cytology tests, within a 10 year period. There are no specific data to support these recommendations.

Colon Cancer Screening

Burden of Suffering

Colorectal cancer (CRC) is the third most common type of cancer in the United States and ranks only behind lung cancer in total cancer deaths. In 2000, it is estimated that there were approximately 130,200 new cases of CRC with 56,600 deaths from the disease.

Mortality from CRC has been decreasing over the past 20 years. This decrease is probably in part due to the advent of screening, although some benefit may be due to improved treatments. Survival rates are strongly dependent on stage at diagnosis, ranging from 92% 5-year survival for localized disease to 8% in those with metastatic disease. In addition, there is racial variation in survival; overall 5-year survival is 62% in white patients and 52% in African-Americans.

Rationale for Recommendations

CRC is a common disease, and frequently is asymptomatic in its early stages. Because symptomatic CRC is sometimes advanced and incurable, screening can impact mortality by detecting lesions in an earlier treatable stage. In addition, it is estimated that the majority (60-90%) of CRC arises from adenomatous polyps. Removal of adenomatous polyps has been shown to decrease the incidence of developing CRC. Thus, screening has impact on CRC through two mechanisms: early detection of malignant lesions, and prevention of CRC development through detection and removal of premalignant adenomatous polyps.
There are at least 4 modalities that are commonly recommended for CRC screening: fecal occult-blood testing (FOBT), flexible sigmoidoscopy (FS), barium enema (BE), and colonoscopy. Various combinations of these tests, particularly of FOBT and FS, have also been proposed. Each of these approaches vary in sensitivity and specificity in detecting CRC and polyps. Colonoscopy generally is considered the gold standard, although studies repeated in the same patients demonstrate that a single colonoscopy can miss 5-15% of polyps, depending on the size of the lesion. The miss rate for polyps that are significant (>10 mm) is generally less than 5% with colonoscopy. Barium enema misses about 15% of significant polyps. Flexible sigmoidoscopy has similar detection rates to colonoscopy when lesions are within reach of the sigmoidoscope; however, it can only screen the distal colon, and thus will miss nearly half of adenomas. Digital rectal exam is not recommended for screening because fewer than 10% of cancers are within digital reach.

**Fecal occult-blood testing (FOBT).** FOBT is an insensitive and non-specific test in most series, with sensitivity in the 10% range for polyps, with about 5% false-positive rates. To date, only FOBT has had efficacy evaluated in randomized, controlled clinical trials. These studies showed CRC mortality reductions of 15 to 33%. Although screening protocols varied, these studies provide clear evidence that CRC mortality can be reduced with a mass FOBT screening program. However, FOBT has come under criticism due to its low sensitivity and specificity, low patient compliance, and the possibility that FOBT does little more than randomly assign subjects to receive colonoscopy.

**Flexible sigmoidoscopy (FS).** There are several ongoing randomized trials of FS as a screening method for CRC. Case-control studies of FS suggest that exposure to sigmoidoscopy within 10 years is associated with a 59-80% reduction in CRC mortality from cancers within reach of the sigmoidoscope, but this benefit was not seen for patients who developed proximal cancers. The protective effect of FS appears to be between 6 and 10 years in these studies, suggesting that screening at least every 10 years, and possibly as frequently as every 5, is desirable. The main criticism of screening with FS is that it reaches only about half of colonic lesions (adenomas and cancers); in addition, there is now a trend towards increasing prevalence of proximal malignancies. While this may in part reflect the increasing use of FS, it may also suggest that FS will become less effective if the trend continues.

**Colonoscopy and barium enema (BE).** Studies on screening colonoscopy and BE are limited. There are no observational studies of BE in the literature. One case-control study of colonoscopy suggested that exposure to colonoscopy is associated with a 39% reduction in risk of developing CRC. In addition, colonoscopy is the main follow-up intervention in the FOBT screening trials, and therefore is the final pathway that leads to the effectiveness of CRC screening; it is almost certain to be an effective test, but is more costly than other screening modalities.

**Screening modalities in development.** Stool DNA test and virtual colonoscopy are under study. They are not yet commonly available for routine screening.

**Cost-effectiveness of screening.** A number of cost-effectiveness simulation models of screening for CRC have been published. There are a number of different approaches to simulating costs and effectiveness, but it appears that under a variety of baseline assumptions, screening for CRC is cost-effective when compared to other commonly accepted medical interventions.

The most complete and current recommendations for screening the average risk patient were made in 2003 by representatives of the U.S. Multisociety Task Force on Colorectal Cancer, a combined effort of the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, the American College of Physicians/Society of Internal Medicine, and the American Gastroenterological Association. Recommendations for screening average risk people are summarized in table 3. All of these options are considered viable alternatives for CRC screening.

Individualizing screening to offer the highest likelihood of compliance and the least intrusive option to the patient may be warranted. In addition to patient preference, other factors, such as age, comorbidities, and test availability may influence the choice of screening modality.

**Screening for High-Risk Patients**

Screening in patients with elevated risks of CRC is likely to be more effective and cost-effective than screening the general population. High-risk patients, and their screening, can be classified into several categories. There is little specific data evaluating interventions in most of these groups, however, so that expert opinion is generally the guide for these screening protocols. Recommendations of the U.S. Multisociety Task Force on Colorectal Cancer for screening high-risk people are presented in Table 4.

**Prostate Cancer Screening**

**Burden of Suffering**

Prostate cancer is an enigmatic disease with a course ranging from a symptom-free, indolent condition without morbidity or effect on life to a virulent cancer with rapid progression to bone metastases and death. Between these two extremes lies a spectrum of manifestations that pose varying levels of threat to men’s life spans & quality of life. Prostate cancer is the most commonly diagnosed non-cutaneous cancer among men in the United States and ranks second only to lung cancer in the number of cancer-related deaths among men. In 2000, it is estimated that approximately 180,400 new cases will be diagnosed nationwide, and 37,000 men will die from the disease. Although there has been an overall increase in mortality over the past 20 years, a consistently decreasing mortality...
rate has been reported since 1998.

Table 3. Colon Cancer Screening for Average-risk People above Age 50

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOBT (^a)</td>
<td>Annual</td>
<td>Two samples from each of 3 consecutive stools</td>
</tr>
<tr>
<td>FS</td>
<td>Every 5 years</td>
<td>Only evaluates distal colon directly</td>
</tr>
<tr>
<td>FOBT (^a) / FS</td>
<td>Annual/Every 5 years (FOBT 1st)</td>
<td>Allows some evaluation of entire colon</td>
</tr>
<tr>
<td>Double-contrast barium enema</td>
<td>Every 5 years</td>
<td>Least well-evaluated method of screening</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
<td>“Gold-standard” test</td>
</tr>
</tbody>
</table>

\(^a\) To decrease false positive FOBT results, for 7 days before and during FOBT patients should avoid non-steroidal anti-inflammatory drugs, e.g., ibuprofen, naproxen or aspirin (more than one adult aspirin a day) and for 3 days avoid red meats, vitamin C supplements, or citrus fruits and juices. Women should not perform the test during menstruation.

Table 4. Colon Cancer Screening for People at Higher Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial Risk</strong></td>
<td></td>
</tr>
<tr>
<td>One second-degree (^a) or any third-degree relative (^b) with colorectal cancer</td>
<td>Same as average risk</td>
</tr>
<tr>
<td>First-degree relative (^c) affected with colorectal cancer or adenomatous polyp at age ≥ 60 years, or 2 second-degree relatives affected with colorectal cancer</td>
<td>Same as average risk, but starting at age 40 years</td>
</tr>
<tr>
<td>Two or more first-degree relatives with colon cancer, or a single first-degree relative with colon cancer or adenomatous polyps diagnosed at an age &lt; 60 years</td>
<td>Colonoscopy every 5 years, beginning at age 40 years or 10 years younger than the earliest diagnosis in the family, whichever comes first.</td>
</tr>
<tr>
<td>Gene carrier or at risk for familial adenomatous polyposis (^d)</td>
<td>Sigmoidoscopy annually, beginning at age 10-12 years (^e)</td>
</tr>
<tr>
<td>Gene carrier or at risk for HNPCC</td>
<td>Colonoscopy, every 1-2 years, beginning at age 20-25 years or 10 years younger than the earliest case in the family, whichever comes first.</td>
</tr>
<tr>
<td><strong>Personal Risk</strong></td>
<td></td>
</tr>
<tr>
<td>History of adenomatous polyps, for example:</td>
<td>Manage according to the findings and clinical judgment, e.g.:</td>
</tr>
<tr>
<td>1 or 2 small (&lt; 1 cm) tubular adenomas</td>
<td>First follow-up colonoscopy at 5 years</td>
</tr>
<tr>
<td>Advanced or multiple adenomas (≥ 3)</td>
<td>First follow-up colonoscopy in 3 years</td>
</tr>
<tr>
<td>History of colorectal cancer</td>
<td>Timing of subsequent colonoscopy depends on findings at follow-up.</td>
</tr>
<tr>
<td>Inflammatory bowel disease (ulcerative colitis, Chron’s colitis)</td>
<td>After colonoscopy to rule out synchronous neoplasms and resection with curative intent, first follow-up colonoscopy after 3 years, and then, if normal, every 5 years.</td>
</tr>
<tr>
<td>In patients with long-standing, extensive inflammatory bowel disease, surveillance colonoscopy with systematic biopsies should be considered.</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Second-degree relatives include grandparents, aunts, and uncles.
\(^b\) Third-degree relatives include great-grandparents and cousins.
\(^c\) First-degree relatives include parents, siblings, and children.
\(^d\) Includes the subcategories of familial adenomatous polyposis, Gardner syndrome, some Turcot syndrome families, and attenuated adenomatous polyposis coli (AAPC).
\(^e\) In APPC, colonoscopy should be used instead of sigmoidoscopy because of the preponderance of proximal colonic adenomas. Colonoscopy screening in AAPC should probably begin in the late teens or early 20s.
The likelihood of dying from prostate cancer varies for different segments of the population. National mortality data collected between 1989 and 1993 show that only 2.9 per 100,000 men under the age of 65 died from prostate cancer, compared with 240.6 for men over 65 years of age. Similar findings are observed in Michigan as well. At all ages, African-American men die more often from prostate cancer than do white men. With the exception of African-American men age 85 and older, the same is true for men in Michigan.

Clinicians need to understand the current evidence regarding benefits and risks of screening and help patients make informed decisions to be or not to be screened.

**Rationale for Recommendation**

There is considerable controversy surrounding screening for prostate cancer. Early detection and treatment may avert future prostate cancer-related illness, but treatment includes some risk of sexual dysfunction and incontinence and a small risk of treatment-induced mortality. At this time, no trials of sufficient power are available to document the benefit of aggressive treatment (e.g. surgery, radiation) versus conservative management and hormonal therapy. Similarly, there is no conclusive evidence that routine screening for prostate cancer is beneficial, and there is no consensus concerning the role of digital rectal examination and PSA testing in screening.

**Digital rectal examination (DRE).** Traditionally, the digital rectal examination (DRE) has been considered a routine screening modality for prostate cancer. Although DRE can successfully detect some prostate cancers, it is less effective in detecting tumors deep within the prostate gland, and its impact on prostate cancer mortality has been shown to be limited. DRE has a significant subjective component that is manifested by only fair inter-examiner agreement. In addition, it has been suggested that 25-35% of prostate cancers occur in areas of the prostate not accessible to the examining finger. The sensitivity of DRE ranges from 18 to 68% with significantly lower specificity. A case-control study and a cohort study demonstrated no significant impact of screening DRE on prostate cancer mortality.

**Prostate-specific antigen (PSA).** Measurement of prostate-specific antigen (PSA) is a common screening test for prostate cancer. Elevations in PSA have been associated with prostate cancer. Using a PSA cutoff value of greater than 4 ng/ml has a sensitivity of over 80%, specificity 29-91%. It is estimated that single elevated PSA measurement can detect nearly 80% of all aggressive cancers diagnosed 5 years before their clinical appearance and approximately 50% of all aggressive cancers diagnosed 9 to 10 years before their clinical appearance. PSA is generally specific to prostate tissue; however it is not specific to only prostate cancer. Older men may develop benign prostatic hyperplasia which often elevates PSA, and hence, the specificity of PSA decreases with age. This has lead some authors to propose age-specific ranges in order to increase the clinical utility of PSA testing. Clinically important elevation of PSA is not seen if DRE is done shortly before the blood is drawn.

The combined use of DRE and PSA is one approach to decrease false positive results. If both the DRE and PSA are suspicious, the positive predictive value of an elevated PSA increases from 32% to 49%, however this significantly reduces sensitivity.

Appropriate follow-up tests for abnormal tests to screen for prostate cancer include transrectal ultrasound and needle biopsy of the prostate.

**Outcome without intervention.** The arguments for and against widespread screening and treatment rely on inferences of the natural history of conservatively managed localized prostate cancer. Survival in men with early stage disease (clinically localized, low grade) treated conservatively appears to be comparable to untreated men. These studies have focused primarily on older men and have documented relatively modest disease-specific mortality among men with low-grade and moderate-grade tumors. Other studies have shown that men with moderate to high-grade tumors have significantly mortality if left untreated.

A population-based, retrospective cohort study evaluated the age-specific, all-cause mortality, disease-specific mortality, and life expectancy for men 65 to 75 years who were treated only with immediate or delayed hormonal therapy for newly diagnosed, clinically localized prostate cancer. Compared with the general population, men aged 65 to 75 years with conservatively treated low-grade prostate cancer incur no loss of life expectancy. Men with higher-grade tumors (Gleason scores 5 to 10) experience a progressively increasing loss of life expectancy. They estimate the loss of life is probably no greater than 4 to 5 years for moderate-grade tumors and 6 to 8 years for high-grade tumors. A competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer concluded that men with Gleason score 2 to 4 disease face minimal risk of death from prostate cancer within 15 years of diagnosis. However, men whose biopsy specimens show Gleason score 7 to 10 disease face a high risk of death from prostate cancer when treated conservatively, even when cancer is diagnosed as late as age 74. Men with Gleason score 5 to 6 tumors face a modest risk of death from prostate cancer that increases slowly over at least 15 years of follow-up. An additional population-based study confirmed a potential benefit of curative therapy among patients with life expectancy greater than 10 years.

A single randomized trial reported in 1981 of expectant management versus surgery did not reveal a significant difference in survival rates. However, this study has been criticized for having small sample sizes and lack of power. Large prospective randomized studies are underway, however the results will not be available for some time.

**Does early detection and treatment alter outcome?**

Although conclusive evidence is lacking, some
epidemiologic data suggest that screening may be altering the natural history of the disease. As would be expected from a successful screening strategy, initial increases in the incidence of localized disease, followed by decreases in advanced disease and a trend toward lower mortality rates, have been observed in several population-based studies carried out since PSA screening was introduced.

**Does PSA screening result in overtreatment of clinically insignificant disease?** A review of 896 radical prostatectomy cases for clinically localized prostate cancer between 1988 and 1996 examined found that, although there was an increase in new cases of prostate cancer during this period, there were no significant changes in cancer volume, tumor grade, serum PSA, or the prevalence of very small tumors (<0.5 cc). These data suggest that PSA testing not has resulted in the detection and treatment of clinically insignificant cancer.

**Cost/Benefit of screening.** In the absence of randomized clinical trials, decision analysis models to evaluate the effectiveness of prostate cancer screening and treatment have found little or no benefit. In these studies, the benefits of screening diminish considerably as the probability of metastasis and treatment effectiveness decrease. However, these analyses rely on untested assumptions about the prognosis of clinically localized cancer and the effectiveness of aggressive treatment. Decision analyses also indicate that, although men 50 to 70 years old will potentially benefit the most from PSA screening, this benefit will not be realized until they are in their seventh or eighth decade of life.

**High risk groups.** First-degree relatives of men with prostate cancer and African-American men have been shown to have a higher lifetime risk for developing prostate cancer. These men should be informed that they are at higher risk for developing prostate cancer. Earlier (starting at age 40) testing may be indicated although benefits have not been shown for these groups.

**Strategy for Literature Search**

The literature searches for this project were conducted prospectively on Medline for literature published since 1/1/95. A search was performed using the major key words adults, humans, English, plus the terms described below for each topic. (The specific key words associated with a term are detailed in parentheses following the first time a term is used.) The searches were conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The searches were supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The searches were single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

**Breast cancer screening.** The additional search terms (with specific key words in parentheses) were: breast cancer (breast neoplasms, mammary neoplasms, experimental mammary neoplasms, breast AND cancer), preventive services (preventive health services, diagnostic services, mass screening, genetic screening, mass chest x-ray, multiphasic screening, neonatal screening, mobile health units, early intervention/education, health education, health fairs, patient education, prevention and control), diagnosis (sensitivity and specificity, predictive value of test, false negative reactions, false positive reactions, likelihood functions), guidelines (clinical protocols, physician’s practice patterns, algorithms, outcome and process assessment [health care], consensus development conferences, guideline, practice guidelines), research studies (clinical trials, clinical trials – phase IV, randomized clinical trials, controlled clinical trials, multicenter studies, cohort studies).

**Cervical cancer screening.** The additional search terms were: cervical cancer (cervical neoplasms, cervical intraepithelial neoplasms, cervix dysplasia), preventive services, diagnosis, guidelines, research studies.

**Colon cancer screening.** The additional search terms (with specific key words in parentheses) were: gastrointestinal cancer (gastrointestinal neoplasms, intestinal neoplasms, stomach neoplasms), preventive services, diagnosis, guidelines, research studies.

**Prostate cancer screening.** The additional search terms were: prostate cancer (prostatic neoplasms), preventive services, diagnosis, guidelines, research studies.

**Disclosures**

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.
Annotated References

Breast cancer screening:


A comprehensive review of evidence and updated recommendations regarding screening for breast cancer. It includes a description of the methodology used to identify and rate evidence as well as projections of benefits and harms of implementing the recommendations on a population basis.

Cervical cancer screening


A comprehensive review of evidence and updated recommendations regarding screening for cervical cancer. It includes a description of the methodology used to identify and rate evidence as well as projections of benefits and harms of implementing the recommendations on a population basis.

Colon cancer screening:


A comprehensive review and update is presented for recent findings concerning the methods of screening for colorectal cancer. It includes important reviews of the epidemiology, test characteristics, test effectiveness, and cost-effectiveness of screening. While the costs and efficacy of different procedures vary, screening should be performed. Choice of modality is the preference of the provider and patient.

Prostate cancer screening


A comprehensive review of evidence and updated recommendations regarding screening for prostate cancer. It includes a description of the methodology used to identify and rate evidence as well as projections.
<table>
<thead>
<tr>
<th>Screening Procedure</th>
<th>20 -</th>
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<th>50 -</th>
<th>70</th>
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<td><strong>Women</strong></td>
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<td>Mammography</td>
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<tr>
<td>Pap Smear: Start 3 years after intercourse or at age 21</td>
<td>Depending upon risk factors and family history</td>
<td>Every 1-2 years weaker &amp; benefit than in age less than</td>
<td>Every 1--2 years</td>
<td>Base on life expectancy</td>
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<td>Pap Smear</td>
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<td>Annually for conventional pap, every 2 years for thin prep</td>
<td>Every 2-3 years if low risk; annually if high risk</td>
<td>If 3 normal paps in last 10 years &amp; low risk, stop at age 65 or 70</td>
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<td><strong>Men</strong></td>
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<td>Prostate specific antigen</td>
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<td>Digital rectal examination</td>
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<td>Both men and women</td>
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<td>Colonoscopy OR</td>
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<td>Flexible sigmoidoscopy AND/OR</td>
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<td>Fecal occult blood test</td>
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<td>Earlier and more frequently based on risk factors</td>
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<td>Base on life expectancy</td>
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