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Cancer Screening

Population: Adults, 18 years and older

Objectives: Implement an evidenced-based strategy for screening adults for cancers of the breast, cervix, colon, and prostate.

Key Points

Breast Cancer Screening

Modalities. Mammography with or without clinical breast exam.

Current controversies. Whether to screen women ages 40-49.

Initiate.

Average risk. Routine screening mammography should be offered to women ages 50-74 *[I A*]*. For women ages 40-49, two nationally recognized recommendations are:
- The American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) recommend beginning screening at age 40 years for average-risk women *[II B]*.
- US Preventive Services Task Force (USPSTF) recommends that beginning screening before the age of 50 years should be an individual decision that takes patient context into account, including the patient's values regarding specific benefits and harms. For women ages 40-49 use shared decision making, including a discussion of the potential benefits and risks of screening mammography *[I B]*.

High risk. Women at increased risk of breast cancer may benefit from earlier screening and discussion of risk reduction strategies (see Tables 2–3) *[II B]*.

Frequency. For average-risk women, ACS and NCNN recommend screening every year; USPSTF recommends screening every two years *[II C]*. For high risk, see Table 3.

Terminate. Consider continuing screening over age 74 only if life expectancy > 10 years *[IIB]*.

Cervical Cancer Screening

Modalities. Liquid-based cervical cytology (ThinPrep®) and conventional Papanicolaou (Pap) smear of cervical cells are acceptable for screening. Co-testing using a combination of cytology (Pap) and HPV DNA testing may be appropriate for women older than 30 years.

Initiate. Start screening at age 21*[I B]*, including women who have received the HPV vaccine *[1C]*. Screening is not indicated for women who have undergone a total hysterectomy for benign indications and do not have a prior history of cervical cancer or its precursors *[III B]*.

Frequency.

Average risk. In women aged:

< 21 years, do not screen

21-29 years, cytology screen every 3 years.

≥ 30 years, screen either every 3 years with cytology or every 5 years with combination cytology and HPV testing. *[1 B]*.

High risk. For women with initial concurrent HPV-positive and cytology-negative screening results, HPV and cytology retesting is recommended in 12 months rather than immediate colposcopy *[II D]*. When available, HPV genotype-specific testing for HPV 16 or HPV 16/18 may be performed for women who are cytology negative and HPV-positive. For women treated for CIN 2 or CIN 3, if surveillance testing (usually cytology 6 months post treatment) is negative, regular screening resumes, as for average-risk women *[1 C]*. More frequent screening, usually annual cytology, with or without HPV testing, is recommended for women who are immunosuppressed, infected with human immunodeficiency virus (HIV), or were exposed to diethylstilbestrol (DES) in utero *[IC]*.

Terminate. Discontinue screening women past age 65 who are not at high risk for cervical cancer and who have three consecutive negative cytology results or two consecutive negative co-tests within the 10 years before cessation of screening, with the most recent test occurring within the past 5 years *[1 C]*. For women who have a history of CIN 2 or CIN 3, continue screening for at least 20 years after initial post-treatment surveillance *[1 C]*. For other high-risk women, screening continues until limited life expectancy no longer warrants *[1 D]*.

Key Points continue onto next page

Note: Appendix A graphically presents cancer screening intervals by patient age.
* **Strength of recommendation:**
  I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
* **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

Colorectal Cancer Screening
Modalities. Recommended modalities include: fecal occult-blood testing (including fecal immunohistochemical testing), flexible sigmoidoscopy, colonoscopy, or stool DNA test. (Digital rectal exam is not effective in screening for colorectal cancer.)
Current controversies. Newer technologies, such as CT colonography (virtual colonoscopy) are not yet fully validated or recommended for average-risk patients.
Initiate. For asymptomatic patients.
  Average risk. Screening should begin at age 50 *[IB]*.
  High risk. Individuals at increased risk of colorectal cancer should undergo more aggressive screening. The age to begin screening varies with the nature of the increased risk – see Table 5 *[IC]*.
Frequency.
  Average risk. Screen with one of the following. The frequency of screening has not been fully evaluated in clinical trials.
  • High-sensitivity fecal occult blood test (FOBT or immunohistochemical test)) annually *[IA]*,
  • Flexible sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years *[IA]*.
  • Colonoscopy every 10 years *[IB]*.
  • Stool DNA testing (Cologuard) every 3 years. Note: Stool DNA testing includes fecal immunochemical testing along with testing for DNA mutations from colon cells *[IA]*.
  High risk. Screening frequency varies with the nature of the increased risk – see Table 5 *[IC]*.
Terminate. Current guidelines suggest discontinuing screening at age 75 *[IB]*. Earlier termination may be considered based on comorbidities and shortened life expectancy.

Prostate Cancer Screening
Modalities. Prostate-specific antigen (PSA) and digital rectal examination (DRE).
Current controversies. USPSTF recommends against PSA screening for average-risk men of all ages because the small potential benefit does not outweigh the significant potential harm *[III C]*. The ACS recommends discussing screening at age 50 for men at average risk. The American Society of Clinical Oncology recommends that for men with life expectancy > 10 years, shared decision making occur because individuals may value some benefits over some harms *[IID]*.
Initiate. If prostate cancer screening is considered, an informed decision-making process should precede a decision to perform screening *[I A]*. Clinicians should share decision making with men, giving information about the uncertainties, risks, and potential benefits of prostate cancer screening.
  Average risk.
  - For men ages 50-74 with a life expectancy > 10 years, clinicians may choose to initiate or not to initiate a shared decision-making discussion about routine screening with patients *[II C]*.
  - When individual patients request PSA screening, clinicians should initiate a shared decision-making discussion *[II C]*.
  High risk. For African-American men and men with a family history of prostate cancer, provide information and discuss PSA screening starting at age 40 *[II C]*.
Frequency. If performed, screening every 1 versus every 4 years results in similar prostate cancer detection rates *[II B]*.
Terminate. If performed, stop screening at age 75, or when life expectancy is < 10 years based on age and health status *[II D]*.

Breast Cancer Screening

Clinical Background

Breast cancer is the most common non-cutaneous cancer in women in the United States. An estimated 192,370 new cases and 40,170 deaths occurred in 2009. 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, and African-American women have the highest case fatality rates.

With the widespread adoption of screening mammography, the number of reported cases of breast cancer has increased 36% in the past 20 years. However, a decline in breast cancer incidence since 2003 may relate to the discontinuation of hormone replacement therapy and may also be due to reduction in mammogram screening rates.

The number of women with detected ductal carcinoma in situ (DCIS) dramatically increased (750%) in the past two decades. Since it is not yet possible to predict which cases of DCIS will progress to invasive breast cancer, all DCIS tumors are currently treated with mastectomy or some combination of lumpectomy, radiation, and tamoxifen, which may represent over-diagnosis or over-treatment.

Breast cancer mortality rates declined by 1.4% per year from 1989-1995 and by 3.2% afterwards. Between 1990 and 2006, the cumulative reduction was 30%. This reduction is probably a result of many factors, including early detection and treatment, especially the application of adjuvant chemotherapy and anti-hormonal therapy.

Rationale for Recommendations

Benefits and potential harms of screening. Screening has demonstrated benefit, but also increases the potential for some types of harms.

Effectiveness of screening. Screening reduces breast cancer death. The relative risk of breast cancer death among women of all ages (39-74) randomized to mammographic screening invitation in eight prospective randomized controlled trials was 0.84 (95% CI, 0.77-0.91).
The decreases in relative risk for death due to breast cancer for women ages 39-49 years and 50-59 years are similar, at 0.85 and 0.86, respectively. The evidence for screening is strongest in women ages 60-69, with a relative risk reduction of 32% (RR, 0.68) for invited women. Only 1 study provided data on women older than 70 years, yielding an RR of 1.12, although an RR of 0.78 was found for women ages 65-74 years by combining the results of 2 studies.

Harms of screening. The potential harms are primarily associated with false positive readings. They necessitate further evaluation with additional imaging studies and biopsies, and have been shown to increase anxiety and psychological distress. Also, a small possibility exists for radiation from mammograms to cause breast cancer. Annual mammography of 100,000 women for 10 consecutive years, beginning at age 40, is estimated to result in up to 8 radiation-induced breast cancer deaths.

Screening considerations by age group. The potential benefits and harms of screening shift as women age. Evidence and recommendations are the clearest for women ages 50-74. Opinions range more widely regarding screening for women ages 40-49 and women over 74 years.

Screening women ages 50-74. All major professional organizations recommend routine screening for women in this age range. The clearest evidence is available for these women. Due to the increased risk of breast cancer in this age range, the benefit of "life years gained" (LYG) generally outweighs potential harms from screening.

Screening women ages 40-49. Consideration of benefits and harms in this age range is more complex. Prospective randomized controlled trials show that mammography screening invitation reduces breast cancer mortality in women ages 40-49. However, the absolute benefit is smaller than among older women, mainly because the incidence of breast cancer is lower in younger women, even though LYG is greater. For women in their 40s, 1,904 women must be invited to be screened for 10 years to prevent 1 death from breast cancer, compared to 1,339 women ages 50-59, and 377 women ages 60-69.

False positive readings are more common in younger women, both because the tests are less specific and because breast cancer is less common. In one report, although fewer biopsies were done for abnormal mammograms in younger women than in older women (9.3, 10.8, and 11.6 per 1,000 mammograms for women ages 40-49, 50-59, and 60-69

respectively), more of the biopsies were benign in younger women (6.7, 6.1, and 5.2 per 1,000 mammograms for women in their 40s, 50s, and 60s respectively).

Expert groups have weighed somewhat differently the benefits and potential harms of screening women ages 40-49. Focusing on potential benefits, the ACS and the NCCN recommend screening beginning at age 40. Focusing on potential harms, the USPSTF recommends that the decision to start screening mammography before age 50 years should be an individual one that takes into account patient context, including the patient's values regarding specific benefits and harms. The recommendation is for shared decision-making, discussing with the patient the potential benefits and risk of screening mammography for women in this age range.

Screening women over age 74. Older women face a higher absolute risk of breast cancer. However, no women 75 years or older have been included in the multiple randomized controlled trials of breast cancer screening. 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 and over-diagnosis (since screening detects clinically insignificant cancers). The decision to screen a woman in this age group should be based on her general health and consideration of co-morbidities that may severely limit her life expectancy.

Frequency of mammography screening. Screening intervals ranged from 12 to 33 months in the randomized controlled trials on breast cancer screening. No specific mammography screening interval has been definitively determined to be superior. However, in many countries with breast-cancer outcomes similar to those in the United States, biennial screening (every 2 years) is standard.

Screening women more frequently will identify breast cancer more often and produce the benefit of increased life expectancy. For example, projections comparing annual and biennial screening in women ages 40-74 are that screening 1000 women would produce 188 LYG vs. 142 LYG, respectively (Table 1). However, changing from annual to biennial screening is likely to reduce the harms of mammography screening by nearly half (Table 1).

Expert groups have weighed somewhat differently the benefits and potential harms of annual and biennial screening. The ACS and the NCCN recommend screening annually. The USPSTF recommends screening biennially. Because breast cancer in younger women appears to be faster-growing, consider annual mammography in women < 60 years old and every 1-2 years in older women.

Clinical breast examination (CBE). Evidence is insufficient to recommend for or against clinical breast exam for screening, beyond mammogram screening. No screening trials have compared CBE (without mammography) to no screening. The sensitivity of clinical breast exam ranges from 40% - 69%, with a specificity of 88-90%, and a

positive predictive value (proportion of cancers detected per abnormal exam) of 1.5% for women ages 40-49, and 3-4% for women ages 50-59, using mammography and interval cancer as the criterion standard. However, up to 25% of the palpable breast cancers found on clinical breast exam are not visible on mammography and warrant further evaluation with ultrasound and/or breast biopsy. Therefore, clinical breast examination may augment mammography, but cannot be used alone as a routine screening or diagnostic tool. (National expert opinion is to incorporate CBE into special screening procedures for high-risk women – see Women at High Risk for Breast Cancer, below.)

Teaching breast self-examination. A large randomized controlled trial on providing instruction on BSE without mammographic screening revealed no decrease in mortality from breast cancer after 10 years. There were increases in the number of breast biopsies and the number of benign breast lesions detected in women randomized to BSE. Although BSE is no longer recommended as a routine screening method, if a woman detects a breast abnormality, she should bring it to her physician's attention. (National expert opinion is to encourage periodic breast self-exam as part of special screening procedures for high risk women – see Women at High Risk for Breast Cancer, below.)

Magnetic resonance imaging (MRI). MRI, as an adjunct to other breast imaging modalities, has emerged as a useful technology with increased sensitivity in certain high-risk groups. (See "Screening recommendations for high-risk women" below.) While MRI increases sensitivity compared to mammography alone in women at highest risk for breast cancer, it does so at the cost of decreased specificity and an increased need for invasive diagnostic procedures. Moreover, due to the cost of MRI and its lack of demonstrated efficacy (defined as improved early breast cancer diagnosis with reductions in mortality rate), MRI should not be used for screening except in the highest risk. Several groups recommend annual screening MRI imaging as an adjunct to annual mammography in women with a 20% or greater lifetime risk for developing breast cancer, which includes women with a history of chest irradiation (Table 3). At this time an assessment of very high risk and decision to screen with MRI is likely to be better made by a breast specialist and/or genetic counselor. Even with MRI screening, a significant minority of high-risk women will already have axillary metastatic disease at time of detection.

No guidelines have been established for the use of MRI as a diagnostic tool for evaluation of a palpable breast mass. MRI should not be used routinely as a diagnostic tool, although it may have a limited role when specifically requested by a radiologist or breast specialist.

Women at High Risk for Breast Cancer

Risk factors. The risk factors for developing breast cancer are listed in Table 2.

Age is the major risk factor for breast cancer. Approximately 85% of breast cancers occur in women over age 50. 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 or ovarian cancer in a first degree relative (maternal or paternal); prolonged estrogen exposure (early age at menarche, late menopause, nulliparity, and first child after age 30); history of breast biopsies; proliferative benign breast disease; atypical hyperplasia; and radiologically dense breasts.

Racial-ethnic identity contributes to the assessment of breast cancer risk in women ages 40-49. Although the lifetime risk of breast cancer is lower for African-American women compared to white American women, for women younger than age 45 the incidence rates are higher for African-American women. Furthermore, incidence rates of biologically-more challenging patterns of breast cancer (e.g. tumors that are negative for the estrogen receptor, the progesterone receptor, or the HER2/neu marker) are higher for African-American women of all ages, and the frequency of these tumors is highest among premenopausal African-American women. These age- and race/ethnicity-related variations in breast cancer should be considered when making a decision to start mammography screening.

Women who received >15 Gy radiation to the thoracic, mediastinum, hila, axillae, cervical, supraclavicular or total body irradiation (TBI) area especially if done at age 30 or younger, have a 1% annual risk of breast cancer, starting 10 years after irradiation. Menopausal hormone use, obesity, and alcohol intake are associated with an increase in breast cancer. The Women's Health Initiative study revealed a relative risk of 1.26 (CI 1.00-1.59) of invasive breast cancer with combined conjugated equine estrogen and progesterone hormone replacement therapy (HRT). This 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.

Alterations in BRCA1 and BRCA2 genes make women substantially more susceptible to breast cancer than women with wild type genotypes. Consider referring these women to a breast specialist and/or genetic counselor to discuss earlier screening and risk reduction strategies.

However, it should be emphasized that 75% or more of newly diagnosed breast cancers occur in women with no identifiable risk factors other than sex and age. Therefore, lack of risk factors should not be used to withhold screening from women for whom it is otherwise indicated.

Risk assessment. The NCI's Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool/) can be used to calculate a woman's risk of breast cancer in her lifetime and within the next 5 years. Women at high risk (5 year risk > 1.7%) according to this tool should be offered referral to a breast specialist and considered for risk reduction therapy.

The tool uses a statistical method called the Gail model to provide eligibility criteria for prevention strategies. It has been modified to increase its accuracy in African-American women. While it can be used to guide initiation of screening at an earlier age than what might be otherwise indicated (40-45 years), it should not be used to avoid screening in women who are in the appropriate age group for routine screening.

Unfortunately the NCI tool is not applicable to very high-risk women. It can underestimate the risk for women with a previous history of breast cancer, personal history of thoracic radiation, known or suspected genetic mutations (BRCA1, BRCA2, p53, PTEN or others) or a very strong family history of breast cancer.

Projections of breast cancer risk using the Gail model are less certain for non-Caucasian women, although race has less influence on breast cancer risk than other risk factors.

Screening recommendations for high-risk women. Table 3 outlines the NCCN screening recommendations (age, procedure) for several categories of high-risk women.

Table 1. Chances of breast-cancer-related outcomes among 1000 women screened annually or biennially, starting at age 40 or 50 and continuing through age 69 or 74

Screening program			Cumulative consequences of screening program			
Mammogram frequency	**Starting age**	**Ending age**	**Lives saved, number**	**Life-years gained, number**	**False-positive mammograms, number**	**Unnecessary biopsies, number**
Annual						
	40	69	8.3	164	2250	158
	50	69	7.3	132	1350	95
	40	74	10.5	188	2470	173
	50	74	9.5	156	1570	110
Biennial						
	40	69	6.1	120	1250	88
	50	69	5.4	99	780	55
	40	74	8.2	142	1410	99
	50	74	7.5	121	940	66

Adapted and calculated from: Mandelblatt, JS, Cronin, KA, Bailey, S, et al. Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms. Ann Intern Med 2009; 151:738.

Table 2. Risk factors for developing breast cancer

Risk Factors	Low risk	High risk	Relative risk
Deleterious BRCA1/BRCA2 genes	Negative	Positive	3.0 to 7.0
Mother or sister with breast cancer	No	Yes	2.6
Age	30 to 34	70 to 74	18.0
Age at menarche	>14	<12	1.5
Age at first birth	<20	>30	1.9 to 3.5
Age at menopause	<45	>55	2.0
Use of contraceptive pills	Never	Past/current use	1.07 to 1.2
Use of estrogen + progestin replacement therapy	Never	Current	1.2
Alcohol	None	2 to 5 drinks/day	1.4
Breast density on mammography (%)	0	≥75	1.8 to 6.0
Bone density	Lowest quartile	Highest quartile	2.7 to 3.5
History of a benign breast biopsy	No	Yes	1.7
History of atypical hyperplasia on biopsy	No	Yes	3.7

Adapted from Clemons, M, Goss, P. Estrogen and the risk of breast cancer. N Engl J Med 2001; 344:276

Table 3. Screening Recommendations for High-Risk Women*

High Risk Category	Age to Begin Screening	Screening Procedures
5 year risk of invasive cancer ≥1.7% based on NCI Breast Cancer Risk Assessment Tool, available at: http://www.cancer.gov/bcrisktool/	Age 35	Annual mammogram + clinical breast exam (CBE) every 6–12 months; periodic breast self exam encouraged.
LCIS/atypical hyperplasia	After diagnosis of LCIS/atypical hyperplasia	As above; consider MRI for LCIS.
Prior thoracic radiation therapy	8-10 years after thoracic radiation therapy or age 25, whichever occurs last	As above; consider MRI.
Strong family history or genetic predisposition	5-10 years prior to age of diagnosis of earliest index case	Annual mammogram + clinical breast exam (CBE) every 6–12 months, periodic breast self exam encouraged. Consider annual MRI for women with 20–25% or greater lifetime risk.
Known or suspected hereditary breast and ovarian cancer	Age 25	As above.

LCIS = Lobular Carcinoma In Situ

* From: National Comprehensive Cancer Network Breast Cancer Screening and Diagnosis Guidelines, 2011 (http://nccn.org) and American Cancer Society Guidelines for breast screening with MRI as an adjunct to mammography, 2007.

Cervical Cancer Screening

Clinical Background

In 2012, an estimated 12,170 cases of invasive cervical cancer were expected to occur, with about 4,220 women dying from this disease. Pre-invasive lesions of the cervix are detected far more commonly than invasive cancer. The incidence rates of cervical cancer have decreased by more than 50% in the past 3 decades because of widespread screening with cervical cytology.

Women at higher risk for cervical cancer include those of lower socioeconomic status, those with a history of multiple sexual partners, early onset of sexual intercourse (before age 17), infection with human papillomavirus and other sexually transmitted diseases (including human immunodeficiency

virus [HIV]), cigarette smoking, or immunosuppression. Some experts believe that women who are immigrants to the United States from countries where cervical cytology screening is not the norm are an especially high-risk group.

Disparities in cervical cancer incidence and mortality. Underserved, resource-poor and vulnerable populations still exhibit significant racial and ethnic disparities with regard to incidence, mortality and related survival associated with cervical cancer. The incidence is about 60% higher among black women (10.5/100,000) when compared to white women (6.6/100,000). Cervical cancer mortality among black women is the highest (4.7/100,000) of any racial or ethnic group, especially among African-Americans living in the rural South and in some urban areas such as Washington, DC. Hispanics, Native Americans and Vietnamese-Americans also experience relatively higher cervical cancer incidence rates than the average population.

Although African-Americans and Caucasians undergo screening at similar rates, Hispanics undergo screening at a much lower rate than Caucasians. Similarly, women who are less educated (i.e., less than a high school education) or have lower 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, with an associated increase in the incidence of cervical cancer in the elderly.

Rationale for Recommendation

Organized population-based screening programs using cervical cytology have been the most successful strategy for cervical cancer prevention in the United States. Cervical cancer incidence and mortality rates have decreased by 74-75% since the implementation of routine cervical cytology screening with the Pap test in 1949. The introduction of screening programs in unscreened populations has shown to reduce cervical cancer rates by 60-90% within three years of implementation.

Screening is successful in part because of the slow progression of the disease from a precancerous lesion to an invasive cancer over many years. Frequent testing allows early detection and identification of high-grade pre-malignant cytological abnormalities, providing the opportunity to implement effective treatment options before invasive cancer develops.

Screening tests. Screening is age-dependent and is performed with cytology alone or with a combination of cytology and HPV testing (co-testing).

Cytology. The primary screening tests for cervical cancer are conventional Papanicolaou (Pap) smears of cervical cells and liquid-based collection systems (e.g., ThinPrep®).

Liquid-based cytology samples are collected from the cervix in the same manner as a conventional Pap smear; samples of the transformation zone are collected with both the extended tip of a plastic spatula and an endocervical brush. The collection devices for liquid-based cytology are then rinsed into a buffered solution, transported to the laboratory, and the slide is automatically prepared. Liquid-based collection systems have been thought to improve sensitivity over conventional Pap screening. However, the sensitivity and specificity for both screening modalities are similar.

HPV co-testing. Co-testing for HPV offers benefits of increased detection and increased length of screening intervals; potential harms include prolonged surveillance with additional frequent testing if the HPV is persistently positive.

Compared with cytology, HPV testing has greater sensitivity but lower specificity for identification of CIN3+, and it has better reproducibility than cytology. The addition of HPV testing to cytology enhances the identification of women with adenocarcinoma of the cervix and its precursors, and it increases the detection of prevalent CIN3, permitting a longer interval between screens. HPV testing is useful in triaging women with atypical squamous cells of undetermined significance (ASCUS) to help determine who might benefit from referral for colposcopy and who can return to routine screening.

Most episodes of HPV infection and many CIN1 and some CIN2 lesions are transient and will not develop into CIN3 or cancer. The lower specificity of HPV testing leads to more positive screening results from cytology/HPV co-testing than from cytology alone. Some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results. The percentage of U.S. women undergoing co-testing who will have a normal cytology result and a positive HPV result (and who will therefore require additional testing) ranges from 11% among women age 30–34 years to 3% among women age 60–65 years.

Decisions to co-test for HPV require balancing the potential benefits and the harms. The benefits and harms were recently summarized in a guideline produced by the United States Preventive Services Task Force (USPSTF) and in a guideline produced by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (ACS/ASCCP/ASCPS). The information below reflects the views of both groups unless otherwise noted.

The National Comprehensive Cancer Network (NCCN) has guidelines for cervical cancer screening that incorporate those of ACS/ASCCP/ASCPS for average-risk women. Additionally, NCCN provides screening recommendations for high-risk women and follow-up screening for women treated for cervical cancer. The information below regarding high-risk women reflects the NCCN's recommendations.

Whom not to screen. Screening is not recommended for females under age 21 regardless of onset of sexual activity,

women who have never engaged in sexual intercourse, and women who have had a total hysterectomy for a benign gynecological condition. However, women who may not need cervical cancer screening should continue to receive other appropriate preventive health care, including contraception counseling, and screening and treatment for sexually transmitted diseases.

Females under age 21. Studies reveal a low incidence of invasive cancer among younger women. Also, the potential adverse effects of follow-up treatments for abnormal Pap screening in younger women are of concern. Preterm births and related morbidity increase significantly in women previously treated with excisional procedures for cervical dysplasia.

Human papillomavirus is responsible for carcinogenesis in the transformation zone of the cervix. This virus is prevalent in younger females, leading to increased diagnosis of cytological abnormalities on Pap screening in this age group. Human papillomavirus genital infections are commonly acquired after initiation of sexual intercourse, but most of these infections are transient and are cleared by the immune system within 1-2 years of acquisition, without causing significant dysplastic or cancerous changes. However, persistent infections may help to identify those with increased risk of neoplastic transformation.

Recent studies have shown that the most proximal cervical cancer precursor, CIN 3, is uncommon in women under age 25, and it may persist for a decade or more before progressing to invasive disease, allowing multiple opportunities for detection and treatment even with focused screening.

A recent study of healthcare providers showed that many practices are not consistent with major guideline recommendations, including those for cervical cancer screening. The study also suggested that overuse of screening can increase expenses for the health care system, including unnecessary follow-up testing and procedures. Clinicians must also consider the burden of anxiety and life disruptions created by a diagnosis with unclear clinical significance in a younger woman.

Never engaged in sexual intercourse. No direct evidence supports the screening of women who have never engaged in sexual intercourse, as they are not considered to be at risk of developing cervical cancer.

Total hysterectomy. Women who have undergone a total hysterectomy (with removal of the cervix) for benign gynecologic conditions do not need to undergo screening with vaginal cytology, provided they have no prior history of high-grade CIN2/3. However, a health care provider should confirm and document via physical exam and review of the pathology report (when available) that the cervix was completely removed. Women who have had a supra cervical or subtotal hysterectomy should continue cervical cancer screening as per current guidelines.

Screening initiation. Screening should be initiated at age 21 in women for whom screening is appropriate.

Screening frequency and testing method. Screening intervals vary depending on the assessed risk for the individual woman, the woman's age, and the testing method used.

Women at average risk. After initiation of cervical cancer screening with liquid-based cytology or Pap test, screening should be repeated for women aged:

- 21-29 years, screen every 3 years with cytology only. The high prevalence of HPV in women younger than 30 years results in HPV/cytology co-testing producing more harms than benefits.

- ≥ 30 years, screen either every 3 years with cytology alone or every 5 years with cytology and HPV testing. Both the USPSTF guideline and the ACS/ASCCP/ASCPS guideline recognize that either cytology every 3 years or co-testing every 5 years is acceptable. However, the two guidelines differ somewhat in weighing benefits and harms of co-testing in this age group, resulting in a difference in the following two options:

  - USPSTF: "Screen with cytology every 3 years or for women who want to lengthen the screening interval, screen with a combination of cytology and HPV testing every 5 years." More weight is put on the harms associated with the increase in positive results produced by HPV testing and the burden of more prolonged surveillance with additional testing, including prolonged surveillance among women who would otherwise be advised to end screening at age 65 years on the basis of previously normal cytology results alone.

  - ACS/ASCCP/ASCPS: "Screen with cytology and HPV testing ('co-testing') every 5 years (preferred) or cytology alone every 3 years (acceptable)." More weight is put on the benefits of increased disease detection and increased length of screening intervals.

When co-testing is performed, the test results may be discordant.

- Women with HPV-positive, cytology-negative co-tests should not be referred directly to colposcopy. They should be followed with either:

- Repeat co-testing in 12 months. At repeated co-testing, women testing positive on either test should be referred to colposcopy; women testing negative on both tests should return to routine screening.

- Immediate HPV genotype-specific testing for HPV16 alone or HPV16/18. Women testing positive for HPV16 or HPV16/18 should be referred directly to colposcopy; women testing negative for HPV16 or HVP16/18 should be co-tested in 12 months and managed as above for "repeated co-testing in 12 months."

- Women with HPV-negative, ASCUS (atypical squamous cells of undetermined significance) cytology results

should continue with routine screening.

Women at high risk. The NCCN recommends more frequent screening, usually annual cytology with or without HPV testing, for women with a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), or who are immunocompromised (e.g. HIV infection).

In addition to screening, cytology and HPV testing are used for postoperative surveillance following treatment of CIN 2 or 3 lesions. Surveillance cytology is performed 6 months following treatment. (If negative margins, an option is HPV DNA testing at 12 months.) If this follow-up is negative, NCCN recommends resuming routine screening as described above for women at average risk.

Terminating screening. A decision to discontinue cervical cancer screening can be made based on age, risk, and previous screening results.

Women aged > 65 years at normal or unknown risk. 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.

- Stop screening women with evidence of adequate negative prior screening: three consecutive negative cervical cytology tests or two consecutive negative co-tests within the 10 previous years, with the most recent test occurring within the past 5 years. ACS/ASCCP/ASCP notes that screening should not be resumed for any reason, even if a woman reports having a new sexual partner.
- Women in good health who have never been screened or have not had adequate negative prior screening (as defined in the previous paragraph) are likely to benefit from continued screening until adequate negative prior screening is achieved. Then screening should be stopped.

Women at high risk. Screening typically extends beyond age 65 for high risk women as long as they are in good health and do not have a life-limiting chronic condition.

- For women treated for CIN 2, CIN 3, or cancer, NCCN recommends that screening continue for at least 20 years after initial postoperative surveillance.
- For women with other high risk factors (e.g., in utero DES exposure, immunocompromised status), NCCN recommends that screening continue.

HPV testing to clarify specific risks. Testing for high-risk HPV subtypes is used primarily in risk stratification. NCCN addresses this testing in the follow-up for a cytological diagnosis of atypical squamous cells of undetermined significance (ASCUS).

If a woman age 21 or older has a cytological diagnosis of ASCUS on cytology/Pap screening, reflexive HPV testing should be ordered to clarify risk. If the result is positive for high-risk types, refer for colposcopy. If negative, resume routine screening.

Colorectal Cancer Screening

Clinical Background

Colorectal cancer is the third most common type of cancer in the United States and ranks second behind lung cancer in total cancer deaths. In 2010 approximately 142,570 new cases of colorectal cancer occurred, with 51,370 deaths from the disease.

Mortality from colorectal cancer has been decreasing over the past 20 years. This decrease is probably due in part to the advent of screening, although some benefit may be due to improved treatments. Survival rates are strongly dependent on stage at diagnosis, with 5-year survival ranging from 91% in those with localized disease to 11% in those with metastatic disease. In addition, survival varies by race, with overall 5-year survival of 67% in white women and 56% in African-American women. At least some of this variation is due to lack of screening and differential treatment by race.

Rationale for Recommendations

Colorectal cancer is a common disease that frequently is asymptomatic in its early stages. Because symptomatic colorectal cancer is sometimes advanced and incurable, screening can impact mortality by detecting lesions in an earlier, treatable stage. In addition, 60-90% of colorectal cancer arises from adenomatous polyps. Removal of adenomatous polyps can decrease the incidence of developing colorectal cancer. Thus, screening impacts colorectal cancer through two mechanisms: (1) early detection of malignant lesions, and (2) prevention of colorectal cancer development through detection and removal of premalignant adenomatous polyps.

The modalities commonly recommended for colorectal cancer screening include:

- fecal occult-blood testing (FOBT)
- flexible sigmoidoscopy
- colonoscopy
- stool DNA testing.

Other tests, such as barium enema and CT colonography ("virtual colonoscopy") are also available, but are much less widely recommended due to differences in effectiveness, reliability, and cost. Note that while CT colonography is an option, payors may not cover this modality and providers are advised to check on coverage prior to ordering. Combinations of some tests, particularly FOBT and flexible sigmoidoscopy, have also been proposed.

These screening modalities vary in sensitivity and specificity for detecting colorectal cancer and polyps. Colonoscopy generally is considered the "gold standard," although studies repeated in the same individuals demonstrate that a single colonoscopy can miss 5-15% of polyps, depending on the size of the lesions. 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. One-time testing with stool DNA testing identifies approximately 42% of advanced lesions and one-time testing with fecal immunochemical testing identifies approximately 24% of advanced lesions. Digital rectal exam is not recommended for screening because fewer than 10% of cancers are within digital reach.

Fecal occult-blood testing (FOBT). FOBT technology has improved, with newer generation tests (Hemoccult SENSA, immunohistochemical fecal occult blood tests) having polyp sensitivity of about 23-25%, much improved over prior generations of FOBT (5-10%). False positive rates are on the order of 5-8% with the newer tests, but were only about 2% with prior generations of FOBT.

To date, only the older versions of FOBT have been tested for efficacy in randomized, controlled trials. In 3 studies, colorectal cancer mortality reductions ranged from 15-33%, with differences most likely due to differences in screening intervals and in how the tests were performed. These studies provide clear evidence that colorectal cancer mortality can be reduced with a mass FOBT screening program. By extrapolation, the newer, more sensitive tests seem likely to also reduce colorectal cancer mortality.

Stool DNA testing. Stool DNA testing was approved as a CRC screening tool by the FDA and was approved for reimbursement by Medicare in August 2014. Stool DNA testing identifies DNA mutations from colon cells that are excreted in stool samples. As part of stool DNA testing, a fecal immunochemical test is also routinely performed. The sensitivity for CRC is approximately 92% and the sensitivity for advanced polyps is approximately 42%. Stool DNA testing should be repeated every 3 years. There is zero co-pay for Medicare patients with stool DNA testing. The actual cost of stool DNA testing (approximately $300 every 3 years) is similar to the cost of annual fecal immunochemical testing (approximately $75-$125 annually).

There are no randomized controlled trials to test for the efficacy of stool DNA testing for prevention of CRC.

Flexible sigmoidoscopy. Two randomized controlled trials of flexible sigmoidoscopy screening have been published recently. Both trials were based on once-only screening, and follow-up ranged from 7 to 11 years. In the first, population was randomized to screening or not; at 7 years, there were trends towards reductions in colorectal cancer mortality in intention to treat analyses (HR 0.73, 95% CI 0.47, 1.16). In those who attended screening, colorectal cancer mortality was significantly reduced (HR 0.41, 95% CI 0.21, 0.82). This population will continue to be followed for another 8 years, and many expect benefits to become apparent with longer-term follow-up. In the second trial, a population was also offered once-only screening. In this study, the intention to treat analyses showed a significant reduction in colorectal cancer mortality (HR 0.69, 95% CI 0.59-0.82); colorectal cancer incidence was also reduced by 23%. The number needed to treat to prevent one colorectal cancer death was 489.

These trials provide at least moderate support for flexible sigmoidoscopy as a screening modality. Study limitations include that screening was done only once, that protection was limited to distal colorectal cancer, and that the first study has not yet had complete follow up.

Colonoscopy. No randomized controlled trials of screening colonoscopy have been performed. Observational studies have been fairly consistent in showing reductions in colorectal cancer incidence and mortality. However, recent studies have shown that, similar to sigmoidoscopy, colonoscopy may not produce a benefit for proximal lesions. In one study, mortality for distal colorectal cancer was reduced by 67%, but there was no reduction in proximal colorectal cancer mortality. While many experts have advocated colonoscopy as their strongly-preferred test, the possible lack of protection against proximal cancers has raised some doubt about whether it is a more effective test than the less expensive sigmoidoscopy.

Screening modalities in development. CT colonography (virtual colonoscopy) is available in some settings.

CT colonography has suffered from issues of reliability, with different trials and sites reporting widely disparate results on diagnostic accuracy for polyps. A recent Medicare review panel declined to provide coverage for CT colonography on the basis of lower accuracy and a lack of cost-effectiveness relative to other, better-validated tests.

Cost-effectiveness of screening. Several models using different approaches to simulate costs and effectiveness of colorectal cancer screening have been published. Under a variety of baseline assumptions, screening for colorectal cancer is cost-effective when compared to other commonly accepted medical interventions.

Screening initiation, frequency, and termination. The most complete and current recommendations for screening the average-risk adult were made in 2008 by the USPSTF. They concluded that screening should be offered with FOBT, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years.

The frequency of screening depends on the screening modality. USPSTF suggests that the following three screening regimens will be about equally effective in life-years gained:
- High-sensitivity FOBT annually (two samples from each of three consecutive stools)
- Flexible sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years
- Colonoscopy every 10 years

   (Note: To decrease false positive FOBT results, for the 7 days before and during FOBT, both men and women should avoid non-steroidal anti-inflammatory drugs, and for 3 days before and during FOBT should avoid red meats, vitamin C supplements, and citrus fruits and

juices. Women should not perform the test during menstruation.)

USPSTF recommends against screening people over age 75, as the harms, such as colonic perforation or complications of preparation, may outweigh the benefits.

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

Screening People at Higher Risk

Screening people at higher risk of colorectal cancer is likely to be more effective and cost-effective than screening the general population. High-risk individuals can be classified into several categories. However, little specific data exist to evaluate interventions in most of these groups, and expert opinion is generally the guide for high-risk screening protocols. Recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer for screening high-risk people are presented in Table 5.

Table 4. Follow-Up for Positive Colon Cancer Screen
(Other Than Positive Screening Colonoscopy)

If no previous colon cancer screen positive and a positive FIT, flexible sigmoidoscopy, double contrast barium enema, or Cologard, then perform a diagnostic colonoscopy.

If result of diagnostic colonoscopy is:
- Positive, then follow guidelines for surveillance of lesion.
- Negative (with adequate prep), then no further colon screening of any type for 5 years. After 5 years, consider FIT testing, Cologuard, or flexible sigmoidoscopy, but screening colonoscopy should be repeated only once every 10 years.

Prostate Cancer Screening

Clinical Background

Prostate cancer is the most commonly diagnosed cancer among men in the United States, excluding skin cancers, and among men it ranks second to lung cancer in the number of cancer-related deaths. About 1 out of 6 men in the US will be diagnosed at some time with prostate cancer, but only 1 in 34 will die from this disease. In 2012, an estimated 241,740 new cases will be diagnosed nationwide and about 28,170 men will die from the disease.

Several risk factors have been identified. Age is the most important risk factor. Clinically important prostate cancer is uncommon in men younger than 50 years. As men age,

prostate cancer incidence rates in the US increase with each decade up to about age 70, and then decrease. At all ages, African-American men have a higher incidence of prostate cancer and are more likely to die from the disease than white men. Men with a first-degree relative with prostate cancer have a higher lifetime risk of developing prostate cancer, particularly if the relative was under age 60. Poverty increases the risk of advanced-stage prostate cancer. Some studies show that taking 5-alpha reductase inhibitors (e.g., finasteride or dutasteride) may reduce prostate cancer risk, but these medications are not FDA approved for this purpose. Studies of the effects of diet and supplements on prostate cancer risk show inconsistent results.

Prostate cancer has a remarkably heterogeneous natural history, ranging from a symptom-free cancer with a slow course and no 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 and quality of life.

Rationale for Recommendation

Screening methods. Screening may involve prostate-specific antigen measurements and digital rectal exam, with other methods under consideration

Prostate-specific antigen (PSA). Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate. Measurement of total serum PSA has been a common screening test for prostate cancer since the 1980s. PSA testing is simple, objective, reproducible, relatively non-invasive, and fairly low in cost. Although serum PSA levels are normally very low, no PSA value has been identified below which a man can be sure he has no prostate cancer.

Elevations in PSA have been associated with prostate cancer, and PSA testing has increased the detection of early-stage cancers. The conventional PSA screening cutoff of 4.0 ng/mL has been used in many studies. A single elevated PSA measurement over 4.0 ng/mL can detect subsequent cancer with a sensitivity of 71% for the first 5 years of follow up and 91% for the first 10 years of follow up. A prior negative biopsy decreases the risk that an elevated PSA means prostate cancer.

Table 5. Colorectal Cancer Screening for People at Higher Risk

Risk Category	Screening Recommendation
Familial Risk	
One second-degree [a] or any third-degree relative [b] with colorectal cancer	Same as average risk
First-degree relative [c] affected with colorectal cancer or adenomatous polyp at age $\geq$ 60 years, or 2 second-degree relatives affected with colorectal cancer	Same as average risk, but starting at age 40 years
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 < 60 years	Colonoscopy every 5 years, beginning at age 40 years or 10 years younger than the earliest diagnosis in the family, whichever comes first.
Gene carrier or at risk for familial adenomatous polyposis [d]	Sigmoidoscopy annually, beginning at age 10-12 years [e]
Gene carrier or at risk for HNPCC	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.
Personal Risk	
History of adenomatous polyps, for example: 1 or 2 small (< 1 cm) tubular adenomas Advanced or multiple adenomas ($\geq$ 3)	Manage according to the findings and clinical judgment, e.g.: First follow-up colonoscopy at 5 years First follow-up colonoscopy in 3 years Timing of subsequent colonoscopy depends on findings at follow up.
History of colorectal cancer	After colonoscopy to rule out synchronous neoplasms and resection with curative intent, first follow-up colonoscopy at 1 year, then after 3 years, and then, if normal, every 5 years.
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	In patients with long-standing extensive inflammatory bowel disease, surveillance colonoscopy with systematic biopsies should be considered.

From Levin B, Lieberman DA, McFarland B, Smith RA, et al; American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee, 2008.
[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.

Elevated PSA is not specific to prostate cancer. Older men may develop benign prostatic hyperplasia, which can increase PSA, thus decreasing the specificity of PSA testing with age. This has led some to propose age-specific ranges to improve the clinical utility of PSA testing (e.g., see Table 6). Using age-adjusted PSA ranges will increase sensitivity for younger men and specificity for older men, but can lead to more biopsies in younger men and more missed cancers in older men.

Table 6. Age-based PSA Reference Ranges Used at the University of Michigan Health System Laboratories

Age	Normal PSA Reference Range
0 - 49 yrs	0 - 2.5 ng/mL
50 - 59 yrs	0 - 3.5 ng/mL
60 - 69 yrs	0 - 4.5 ng/mL
70 - 150 yrs	0 - 6.5 ng/mL

Various methods have been proposed to improve the performance of PSA for the early detection of cancer, such as percent free PSA, complexed PSA, PSA density of the transition zone, and PSA velocity. In a man with a PSA over 4.0 ng/mL, an elevated PSA velocity (rise in PSA over time) of 0.75 ng/mL/year or higher, using at least 3 PSA values measured over at least 18 months, may warrant a biopsy, although a benefit has not been proven.

Normal biological fluctuations of PSA can cause false positive screening results, so an elevated PSA may need to be confirmed before more invasive testing is performed. The serum PSA remains high during and for several months after a urinary tract infection or a prostate biopsy. However, DRE and recent ejaculation do not cause clinically significant changes in PSA levels. Medications that inhibit 5-alpha reductase (finasteride, dutasteride) will reduce apparent PSA levels by about 50%.

Digital rectal examination (DRE). With PSA now widely available, DRE is rarely used alone as a screening modality. DRE is most helpful in men with an elevated PSA.

Until the late 1980s, digital rectal examination (DRE) was the traditional screening modality for prostate cancer. Although DRE is inexpensive, relatively non-invasive, and 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, 25-35% of prostate cancers occur in areas of the prostate not palpable on DRE.

Other tests. Trans-rectal ultrasound (TRUS) is not useful as a screening test, but is used to guide biopsy and for staging. CT and MRI are not used for screening due to their high cost and poor performance. A urine test for PCA3, an RNA marker more specific for prostate cancer than PSA, is currently being studied; it may be most useful for men with elevated PSA and a prior negative prostate biopsy.

Controversy concerning benefit and potential harm. Clinicians need to understand the current evidence about risks and potential benefits of screening and help men make informed decisions to be or not to be screened.

Although screening tests (PSA and DRE) are able to detect prostate cancer at an early stage, whether early detection and treatment improve health outcomes is unclear, and no conclusive evidence demonstrates that routine screening for prostate cancer is beneficial. Decision analyses indicate that although men ages 50-70 years 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.

By detecting some prostate cancers that would never cause significant clinical problems, screening leads to both over-diagnosis and over-treatment. Subsequent treatment for prostate cancer with surgery or radiation can have permanent side effects, including sexual dysfunction and urinary incontinence, as well as a small risk of treatment-induced mortality. However, many men with low-grade and low-volume prostate cancers may be candidates for less-aggressive approaches, such as Active Surveillance, where curative treatment is delayed pending evidence of disease progression.

Expert groups have weighed somewhat differently the benefits and potential harms of using prostate-specific antigen (PSA) to screen for prostate cancer and produced somewhat different recommendations.

The USPSTF concluded that PSA-based screening should not be performed in men in the general U.S. population because there is moderate certainty that the small potential benefit does not outweigh the significant potential harm. USPSTF recommends that community- and employer-based screening be discontinued. The USPSTF recognizes that some men will continue to request screening and some clinicians will continue to offer it. Clinicians should not offer PSA screening unless they are prepared to engage in shared decision-making leading to an informed choice by patients. Individual patients requesting PSA screening should be provided an opportunity to make an informed choice based on their understanding of the specific benefits and harms.

The American Cancer Society (ACS) recommends that clinicians provide information about the uncertainties, risks, and potential benefits of prostate cancer screening and initiate a discussion about screening at age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years.

The American Urological Association (AUA) recommends:
• Men age 55–69 years of age who are considering PSA should consult with their physician
• PSA testing is not recommended for men ≤ 40 years, men at average risk between ages either 40–54 years or ≥ 70 years, or with less than 10–15 years of life expectancy
• Men outside range of 55–69 who are at higher risk of prostate cancer (e.g., race, family history) should speak to their physician about the benefits and harms of testing.
• When screening is performed, to reduce harms of screening a routine screening interval of two years or more may be preferred over annual screening.

The American Society of Clinical Oncology (ASCO) concluded that because harms do not outweigh benefits in men with a life expectancy > 10 years, clinicians should discuss with these patients whether PSA testing is appropriate for them using a shared decision making approach. ASCO discourages PSA screening in men with a life expectancy < 10 years.

Considering the evidence and the recommendations of these groups:
• PSA screening should not be routinely performed in the general U.S. population.
• PSA screening should not be performed in men with a life expectancy < 10 years.
• For average-risk men ages 55-69 with a life expectancy > 10 years, clinicians may choose to initiate or not to initiate a shared decision-making discussion about routine screening with patients.
• When individual patients request PSA screening, clinicians should initiate a shared decision-making discussion.

Shared decision-making approach. The prostate cancer screening decision is best made in a partnership between the individual and a trusted clinician who can provide objective information about the uncertainties, risks, and potential benefits of screening. (See Table 7)

Table 7. Key Points to Discuss Regarding Screening for Prostate Cancer

- Prostate cancer is an important health issue for men.
- Screening with PSA and DRE detects cancer at an earlier stage than if no screening is done.
- Screening tests can be misleading, with false-positive or false-negative results.
- Experts disagree about whether prostate cancer screening causes more benefit or harm.
- It is not known whether screening will reduce the number of deaths from prostate cancer.
- An abnormal screening result requires a prostate biopsy to determine if that person actually has cancer.
- When prostate cancer is detected, it is difficult to predict who will benefit from treatment.
- Treatments for prostate cancer can cause sexual dysfunction, urinary incontinence, and other health problems.

Adapted from: ACS, Cancer Facts & Figures 2010.

Initiation, frequency, and termination of screening. The USPSTF recommendation against routine PSA-based screening for men of all ages will likely result in many clinicians not offering routine screening and many patients not wanting it. The following information addresses circumstances when screening is offered or wanted.

Initiate discussion about screening. A clinician may choose to consider prostate cancer screening for a man at average risk for prostate cancer who is age 50-74 and has a life expectancy > 10 years, or such a patient may request screening. Screening should not occur without an informed decision-making process. Informed decision making tools are available on-line from the Centers for Disease Control and Prevention at the site: http://www.cdc.gov/cancer/prostate/informed_decision_making.htm.

Frequency of screening. Prostate cancer detection rates are similar for screening frequency intervals of 1 to 4 years. According to the American Urological Association, more frequent screening contributes to the risk of undergoing a biopsy and appears unnecessary for most men.

Terminating screening. If initiated, prostate cancer screening should be stopped at age 75, or sooner in men who have chronic medical problems and a life expectancy of less than 10 years. The length of time needed to experience a mortality benefit from prostate cancer screening is greater than 10 years. Both age and overall health status should be considered when making decisions about screening. Only

about half of men at age 75 have a life expectancy of 10 years or more.

High risk groups. African-American men, and men with a father, brother or son with prostate cancer (especially if onset before age 60), have been shown to have a higher lifetime risk for developing prostate cancer. These men should be informed that they are at higher risk. Earlier discussion and initiation of screening, starting at age 40, may be indicated for these groups, although a benefit has not been proven.

Next steps following abnormal results. Appropriate follow-up tests for abnormal screening results include trans-rectal ultrasound with needle biopsy of the prostate.

Strategy for Literature Search

The literature searches for the previous versions of this guideline were conducted prospectively on Medline. However, in preparing to perform the search to update this guideline the guideline team learned of the ongoing literature surveillance performed by the National Cancer Institute. NCI performs monthly literature searches of Pubmed for the PDQ® (Physician Data Query) Cancer Information Summaries on Screening and Detection (www.cancer.gov/cancertopics/pdq/screening). The updated information is reviewed in meetings of the PDQ® Screening and Prevention Editorial Board (www.cancer.gov/cancertopics/pdq/screening-prevention-board) every other month, with information added to the online summaries shortly thereafter. We requested and received from the Editorial Board Manager a copy of the search strategies they use for cancer screening literature. In summary the major search terms are: screening, risk, morbidity, exclusionary terms for biological research and treatment, and English language. These terms are used for the specific topics of breast neoplasms, cervix neoplasms, colorectal cancer, and prostate cancer. After reviewing the NCI search strategy and the reporting of results in PDQ® summaries, we accepted their strategy and results as the literature search we would use to update our guideline. The results available in the online summaries as of June 2010 were used. The guideline team supplemented the NCI searches with very recent controlled trials known to expert members of the guideline team and its consultants.

The NCI searches are conducted in components each keyed to a specific causal link in a formal problem structure. The NCI searches are single cycle.

Our conclusions were based on prospective randomized controlled 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.

Related National Guidelines

The UMHHC Clinical Guideline on Cancer Screening is consistent with the following national guidelines. (See References for full citations.)

Breast Cancer Screening

ACS. Guidelines for the Early Detection of Cancer, 2010.
ACOG. Breast Cancer Screening, 2011.
NCI. Breast Cancer Screening (PDQ®), 2010.
NCCN. Guidelines for Breast Cancer Screening and Diagnosis, 2009.
USPSTF. Screening for Breast Cancer , 2009.

Cervical Cancer Screening

ACS/ASCCP/ASCP screening guidelines for the prevention and early detection of cervical cancer, 2012.
ACOG. Cervical Cytology Screening, 2009.
NCCN. Cervical Cancer screening, 2012.
NCI. Cervical Cancer Screening (PDQ®), 2010.
USPSTF. Screening for Cervical Cancer , 2012.

Colon Cancer Screening

ACS. Guidelines for the Early Detection of Cancer, 2010.
NCI. Colon Cancer Screening (PDQ®), 2010.
ACS, U.S. Multisociety Task Force, and ACR. Screening and surveillance for early detection of colorectal cancer and adenomatous polyps, 2008.
USPSTF. Screening for Colorectal Cancer, 2008.

Prostate Cancer Screening

ACS. Guidelines for the Early Detection of Cancer, 2012.
AUA. Clinical Guideline on Prostate Cancer Screening, 2013
NCI. Prostate Cancer Screening (PDQ), 2012
USPSTF. Screening for Prostate Cancer, 2012.

Measures of Clinical Performance

National programs that have clinical performance measures of cancer screening include the following.

Centers for Medicare & Medicaid Services:
• Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO)
• Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)
• Quality measures for Accountable Care Organizations (ACO)
National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set (HEDIS)

Regional programs that have clinical performance measures of cancer screening include the following.

Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures (PGIP)
Blue Care Network [HMO]: clinical performance measures (BCN)

These program's clinical performance measures for screening for the four types of cancer addressed in this guideline are summarized below. When programs have measures, the measures are generally similar, although specific details vary (e.g., population inclusions and exclusions). The general measures are summarized below.

Breast Cancer Screening

The percentage of women 40–69 years of age who had a mammogram to screen for breast cancer within 24 months. (GPRO, MU, ACO, HEDIS, PGIP, BCN)

Cervical Cancer Screening

The percentage of women 21–64 years of age who received one or more Pap tests to screen for cervical cancer within the measurement year or the two prior years (36 months). (MU, ACO, HEDIS, PGIP, BCN)

Colon Cancer Screening

The percentage of adults 50–75 years of age who had appropriate screening for colorectal cancer, generally: fecal occult blood test during the measurement year, flexible sigmoidoscopy during the measurement year or the four prior years, colonoscopy during the measurement year or the nine prior years. (GPRO, MU, ACO, HEDIS, BCN)

Prostate Cancer Screening

None of the programs has a clinical performance measure for prostate cancer screening

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.

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Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, General Obstetrics & Gynecology, Breast Oncology, Breast Radiology, Gastroenterology, Gynecology Oncology, and Urology. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

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Appendix A. Screening for Common Cancers:
Minimum Intervals for Preventive Care of Asymptomatic, Apparently Healthy, Low-Risk Adults

Screening Procedures	Age					
	21-29	30-39	40-49	50-59	60-74	75 & older
Women						
Breast Cancer: Mammography	Depending upon risk factors and family history		Annually or shared decision-making	Every 1-2 years		Consider continuing if life expectancy > 10 years
Cervical Cancer: Pap Smear	Every 3 years with cytology only	Every 3 years with cytology or every 5 years with combination cytology and HPV testing				Discontinue >65, not at ↑ risk for CA, with 3 consecutive neg cytology or 2 consecutive neg co-tests within past 10 yrs, with most recent test within past 5 yrs
Men						
Prostate Cancer: Prostate specific antigen and digital rectal examination			If African-American or family history of prostate cancer, shared decision-making	Either: • No screening • Shared decision-making if life expectancy >10 years		
Both Men & Women						
Colon Cancer, either:						
Colonoscopy				Every 10 years		
Flexible sigmoid-oscopy with high sensitivity FOBT	Earlier and more frequently based on risk factors			Flex. sig. every 5 yrs & HS FOBT every 3 years		
High sensitivity FOBT				Annually		
Stool DNA testing (Cologuard)				Every 3 years		