Cancer Screening and Prevention

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LEARNING OBJECTIVES

1. Evaluate the risks and benefits of cancer screening and prevention.
2. Assess the differences in cancer prevention therapies for patients with normal- and high-risk breast cancer.
3. Construct a cancer prevention plan for a patient at risk of breast, colorectal, human papillomavirus–related, or prostate cancer.
4. Distinguish between cancer screening guideline recommendations for breast, cervical, colorectal, lung, and prostate cancers.
5. Design an appropriate cancer-screening plan for an individual patient according to cancer-screening guidelines and individual risk factors.

ABBREVIATIONS IN THIS CHAPTER

ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ACS	American Cancer Society
AUA	American Urological Society
CBE	Clinical breast examination
CRC	Colorectal cancer
DRE	Digital rectal examination
FIT	Fecal immunochemistry test
gFOBT	Guaiac-based fecal occult blood test
HPV	Human papillomavirus
LCIS	Lobular carcinoma in situ
NCCN	National Comprehensive Cancer Network
PSA	Prostate-specific antigen
SERM	Selective estrogen receptor modifier
USPSTF	U.S. Preventive Services Task Force

Table of other common abbreviations.

INTRODUCTION

In 2016, an estimated 1,685,210 new cancers will be diagnosed, and about 595,690 Americans will die of cancer (ACS 2016a). Many cancers can be prevented. Moreover, patients can be screened for cancer to detect and remove precancerous lesions and/or detect cancer early, which reduces morbidity and mortality. Cancer prevention or risk reduction is thought to reduce cancer mortality. This can be accomplished by (1) avoiding carcinogens or altering the metabolism of the carcinogen (e.g., use of dietary or pharmaceutical chemoprevention); (2) modifying lifestyle or dietary practices that alter cancer-causing factors or genetic predispositions; (3) using chemoprevention; or (4) using early detection procedures to remove precancerous lesions. Prevention can be categorized as primary, secondary, and tertiary. Primary prevention includes interventions to prevent the development of cancer (e.g., avoiding carcinogens, modifying lifestyles, using chemoprevention), whereas secondary prevention includes interventions leading to the discovery and control of cancer or precancerous lesions (e.g., screening and early detection). Tertiary prevention is the use of treatment once cancer is diagnosed to reduce the complications and progression or recurrence of cancer.

Several carcinogens have causally been associated with the development of cancer, including cigarette/tobacco use, infections, immunosuppression, and radiation therapy (Box 1-1). Other risk factors that have been implicated in cancer development include diet, obesity, and diabetes. For example, a diet high in fruit and vegetable consumption has been associated with protection against esophageal, mouth, stomach, and possibly lung cancers, whereas a diet high in red and processed meat is associated with an increased risk of developing colorectal and stomach cancer. Because data are limited and often based on observational studies, no specific dietary recommendations are provided; rather, individuals should have a well-balanced diet, much like what one would do to maintain cardiovascular health.

In cancer screening, cancer is found using a procedure or blood test at an early stage, often before symptoms appear. Data vary on the number of premature deaths (3%–35%) that are avoided using screening (NCI 2016). In addition to avoiding premature deaths, screening may reduce cancer morbidity because treatments for early-stage cancers are often better tolerated than those for more advanced-stage cancers and, in some cases, allow for removal of precancerous lesions, such as with colonoscopy.

Box 1-1. Carcinogens Associated with Cancer Development

Cigarette/Tobacco Use

- Acute myelogenous leukemia
- Bladder
- Cervix
- Esophagus
- Kidney
- Lung
- Oral cavity
- Pancreas
- Stomach

Infections

- Epstein-Barr virus
  - Burkitt lymphoma
- *Helicobacter pylori*
  - Gastric
- Human papillomavirus
  - Anal
  - Cervical
  - Oropharyngeal
  - Penile
  - Vaginal
  - Vulvar
- Hepatitis B and C
  - Liver

Immunosuppression

- Non-Hodgkin lymphoma
- Kidney
- Liver
- Lung

Radiation

- Ionizing radiation
  - Breast
  - Hematologic malignancies (i.e., leukemia, lymphoma)
  - Lung
  - Thyroid
- UV radiation
  - Melanoma
  - Nonmelanoma skin cancers

Information from: Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891-901; and National Cancer Institute. Cancer Prevention.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the most common cancers in the United States
- Basic understanding of cancer prevention and screening concepts
- Drug knowledge of agents used for chemoprevention
- Knowledge of general statistical concepts used to evaluate a clinical test

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Cancer Society. Guidelines for Early Detection of Cancer.
- Lalkhen AG. Clinical tests: sensitivity and specificity. Cont Ed Anaesth Crit Care Pain 2008;8:221-3.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
- National Cancer Institute. Cancer Prevention.
- National Cancer Institute. Cancer Screening.

Cancer prevention and screening are not without risks, however, and the potential harms must be considered against the potential benefits (Kramer 2004). The risks of cancer prevention primarily reside in the potential adverse effects or complications of chemoprevention or early detection removal procedures. Cancer prevention strategies may also provide a false sense of protection from cancer because no one preventable strategy is fully protective. Although cancer screening is typically noninvasive or minimally invasive, complications may occur (e.g., perforation during colonoscopy). In addition, false test results may lead to anxiety or unnecessary further testing, which may carry its own risks (false

positive) or falsely reassure an individual who may ignore subsequent signs and symptoms of cancer, possibly delaying diagnosis and treatment (false negative). Overdiagnosis or lead-time bias is also a concern. For example, some prostate cancers are indolent and not clinically important. Diagnosing a slow-growing lesion may then lead to overtreatment and possible morbidity and earlier mortality because of the treatment (overdiagnosis) or have no change at all on mortality (lead-time bias). Lead-time bias can also result in additional morbidity from unneeded treatments and the emotional impact on the diagnosis and treatment.

CANCER PREVENTION

Although prevention of cancer would be ideal, effective prevention strategies are currently available for only some cancers. Cancers for which evidence supports cancer prevention strategies in patients include breast cancer, colorectal cancer (CRC), human papillomavirus (HPV)-related cancers (anal, cervical, penile, vaginal, vulvar cancers), ovarian cancer, and prostate cancer. This chapter focuses on primary prevention of cancer, rather than secondary or tertiary prevention of cancer.

Breast Cancer

Most breast cancers are not related to risk factors other than increasing age and female sex. However, some women are at increased risk because of familial/genetic factors (e.g., breast cancer gene 1 or 2 [*BRCA1* or *BRCA2*), age (e.g., increasing age), ethnicity/race (e.g., Ashkenazi Jewish descent), lifestyle factors (e.g., increased BMI, alcohol consumption), reproductive history (e.g., younger age at menarche, low or nulliparity), and/or disease risks (e.g., history of lobular carcinoma in situ [LCIS] or radiation to thoracic area at younger than 30) (NCCN 2016a). In patients with any of these risk factors who are 35 and older, the Gail model is used to determine the individual's 5-year breast cancer risk (Gail 2001; Spiegelman 2001; Gail 1989). The National Cancer Institute has a freely available risk assessment tool using the Gail model. In women with a calculated 5-year relative risk of 1.7% or higher and a life expectancy of 10 years or more or in those with a known genetic predisposition, such as *BRCA1* and/or *BRCA2* mutation positive, cancer prevention options should be offered, together with a risk-benefit discussion. For these women at higher risk, specific cancer prevention, also sometimes known as risk reduction strategies, can be used. All women could benefit from lifestyle modifications, such as minimal alcohol consumption (less than 1 alcoholic drink per day equivalent to 1 oz of liquor, 6 oz of wine, or 8 oz of beer), a healthy well-rounded diet, and regular exercise to minimize obesity and weight gain. The following discussion of breast cancer prevention focuses on primary prevention only. Although women with a diagnosis of breast cancer may be at an increased risk of developing a contralateral breast cancer, the recommendations that follow do not apply. Instead, women with a diagnosis of breast cancer may typically receive breast cancer treatment that is aimed at reducing the recurrence of cancer anywhere within the body, including in the contralateral breast. For current, specific recommendations on such therapy, the National Comprehensive Cancer Network (NCCN) is a good resource.

Patients with the BRCA1- *or* BRCA2 *Mutation*

Women with the *BRCA1* or *BRCA2* mutation have an estimated lifetime risk of developing breast cancer of 56%–84% (Antoniou 2006; Ford 1998; Struewing 1997). In addition, these women are at a high risk of developing ovarian cancer (36%–46% in *BRCA1* and 10%–27% in *BRCA2*) (Antoniou 2003; King 2003; Satagopan 2002; Prevalence 2000; Ford 1998). With this high risk of developing breast cancer, the use of bilateral mastectomy has been investigated as a cancer prevention strategy. Retrospective analyses have indicated that bilateral mastectomy in *BRCA1* and/or *BRCA2* mutation carriers reduces the risk of breast cancer by at least 90% (Hartmann 2001; Hartmann 1999). A recent meta-analysis of four prospective studies (about 2600 patients) has confirmed a significant risk reduction of breast cancer after bilateral mastectomy (HR 0.07; 95% CI, 0.01–0.44; p=0.004) (De Felice 2015). Similarly, prophylactic bilateral salpingo-oophorectomy is effective in reducing the risk of breast cancer by about 50%, as well as ovarian/fallopian tube cancer by 80% (Rebbeck 2009; Eisen 2005; Rebbeck 2002; Rebbeck 1999). Given these data, the NCCN recommends that bilateral total mastectomy (with or without reconstruction), alone or in combination with bilateral salpingo-oophorectomy, in women with the *BRCA1* or *BRCA2* mutation who desire risk reduction after counseling, as an appropriate cancer prevention option (NCCN 2016a). Risk-reduction agents are not routinely recommended at this time because either no (raloxifene; aromastase inhibitors) or limited (tamoxifen) data in this population exist. (See the section on ovarian cancer for prevention strategies.)

Women 35 and Older

In women 35 and older who have a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the Gail model, chemoprevention with selective estrogen receptor modifiers (SERMs) or aromatase inhibitors may be beneficial as a prevention strategy.

Selective Estrogen Receptor Modifiers

Tamoxifen and raloxifene significantly reduce the risk of breast cancer. In the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1 trial), women 60 and older, pre- or postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the GAIL risk model, and women with a history of LCIS were randomized to tamoxifen 20 mg by mouth daily for 5 years or placebo (Fisher 1998). The short-term risk of developing breast cancer in women 35 and older decreased by 49% at 5 years and 43% at 7 years.

The number needed to treat was 47. In this study, after 7 years of follow-up, a reduction in bone fractures occurred (RR 0.68; 95% CI, 0.51–0.92), but tamoxifen was associated with an increase in pulmonary embolism (RR 2.15; 95% CI, 1.08–4.51), and more cases of endometrial cancer, hot flashes, and cataracts occurred. A slightly higher rate of pulmonary embolism occurred in women older than 50 (RR 2.16; 95% CI, 1.02–4.89) (Fisher 2005). Other chemoprevention studies of tamoxifen in women at higher risk of developing breast cancer have had similar efficacy results (NCCN 2016a).

Raloxifene is a second-generation SERM that has less endometrial stimulation than tamoxifen but similar antiestrogenic activity. In the National Surgical Adjuvant Breast and Bowel Project STAR trial (P-2 trial), postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the GAIL risk model or a history of LCIS were randomized to tamoxifen 20 mg by mouth daily or raloxifene 60 mg by mouth daily (Vogel 2006). After 4 years of therapy, the relative risk of developing breast cancer was similar between the two agents (RR 1.02; 95% CI, 0.82–1.28). However, by 8 years, tamoxifen was more likely to decrease risk (RR 1.24; 95% CI, 1.05–1.47). The raloxifene group had a lower incidence of thromboembolic events, cataract development, and endometrial cancer.

Despite raloxifene's potentially lower incidence of adverse effects, tamoxifen is the preferred chemopreventive agent, especially in younger women, because of its superior long-term efficacy. Tamoxifen can be used in both pre- and postmenopausal women, whereas raloxifene has proven efficacy only in postmenopausal women. Raloxifene, however, may be preferred in postmenopausal women older than 50 with a uterus because it does not increase the risk of endometrial cancer or cataract development (NCCN 2016a). All women should be counseled on the signs/symptoms of thromboembolism. Contraindications for tamoxifen or raloxifene include history of thrombotic conditions (e.g., thromboembolism, thrombotic stroke, transient ischemic attack) or current pregnancy or potential for pregnancy without adequate contraception. Five years of chemoprevention is the current recommendation for these agents, although women may benefit from longer durations.

Aromatase Inhibitors

Aromatase inhibitors (anastrozole, letrozole, exemestane) are effective in the treatment of breast cancer. Furthermore, these agents do not have estrogenic activity, compared with SERMs. Because early treatment trials found that these agents decreased the risk of contralateral breast cancer, they were then evaluated for breast cancer reduction. The Mammary Prevention 3 trial randomized in double-blind fashion women 60 and older, pre- or postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer, or women with a history of atypical ductal or lobular hyperplasia or LCIS to receive exemestane 25 mg or placebo by mouth daily. Those treated with exemestane had a reduction in breast cancer incidence compared with those receiving placebo (HR 0.35; 95% CI, 0.18–0.70) (Goss 2011). The International Breast Cancer Intervention Study II evaluated anastrozole 1 mg by mouth daily versus placebo in a similar high-risk group of women. These results also showed that anastrozole resulted in reduced breast cancer incidence (HR 0.47; 95% CI, 0.23–0.68) (Cuzick 2014). The most common adverse effects reported in these trials were arthritis, arthralgia, and hot flashes. In addition, patients were more likely to develop bone loss and ultimately fracture, given the antiestrogenic activity in bone. Because of these trials, the NCCN breast cancer reduction guidelines recommend either exemestane 25 mg by mouth daily for 5 years or anastrozole 1 mg by mouth daily for 5 years for chemoprevention in postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer or a history of LCIS. Neither of these agents is currently FDA approved for this indication. An aromatase inhibitor for chemoprevention may be appropriate for postmenopausal women with normal or stable bone density or for those with comorbid conditions that preclude the use of a SERM (see Figure 1-1).

Colorectal Cancer

Many studies have evaluated agents for the chemoprevention of CRC in high-risk individuals and those within the general population. Current guidelines, however, recommend the use of aspirin only for chemoprevention.

Aspirin, NSAIDs, and Cyclooxygenase-2 Inhibitors

According to the results of observational studies, taking at least two doses per week of aspirin or an NSAID is associated with a reduced risk of CRC. In an average-risk individual, regular aspirin use (80–320 mg/day) is associated with a 20%–40% reduction in the risk of colorectal adenoma and CRC (Teixeira 2014). In patients with a history of adenomas or diagnosis of CRC, regular daily aspirin use reduces colorectal adenoma recurrence and CRC incidence and mortality. Benefit has also occurred with NSAID and cyclooxygenase 2 (COX-2) inhibitor use, primarily with sulindac and celecoxib. For example, a 30%–45% reduction in the risk of CRC occurred with celecoxib (200–400 mg/day) use over a 10- to 15-year period (Teixeira 2014). In patients with a history of adenomas, combining sulindac (150 mg/day) with ornithine decarboxylase inhibitor difluoromethylornithine (500 mg/day) resulted in a 70% reduction in adenomas, but this was limited by ototoxicity and cardiotoxicity. The protective effects of these agents appear to be related to their inhibition of COX-2 and free radical formation.

However, the optimal dosing and duration of aspirin, NSAIDs, and COX-2 inhibitors remain to be determined, and potential cardiovascular events, gastric ulceration, and bleeding with these agents are possible. Although NSAIDs may be appropriate for selected individuals at a high risk of CRC but

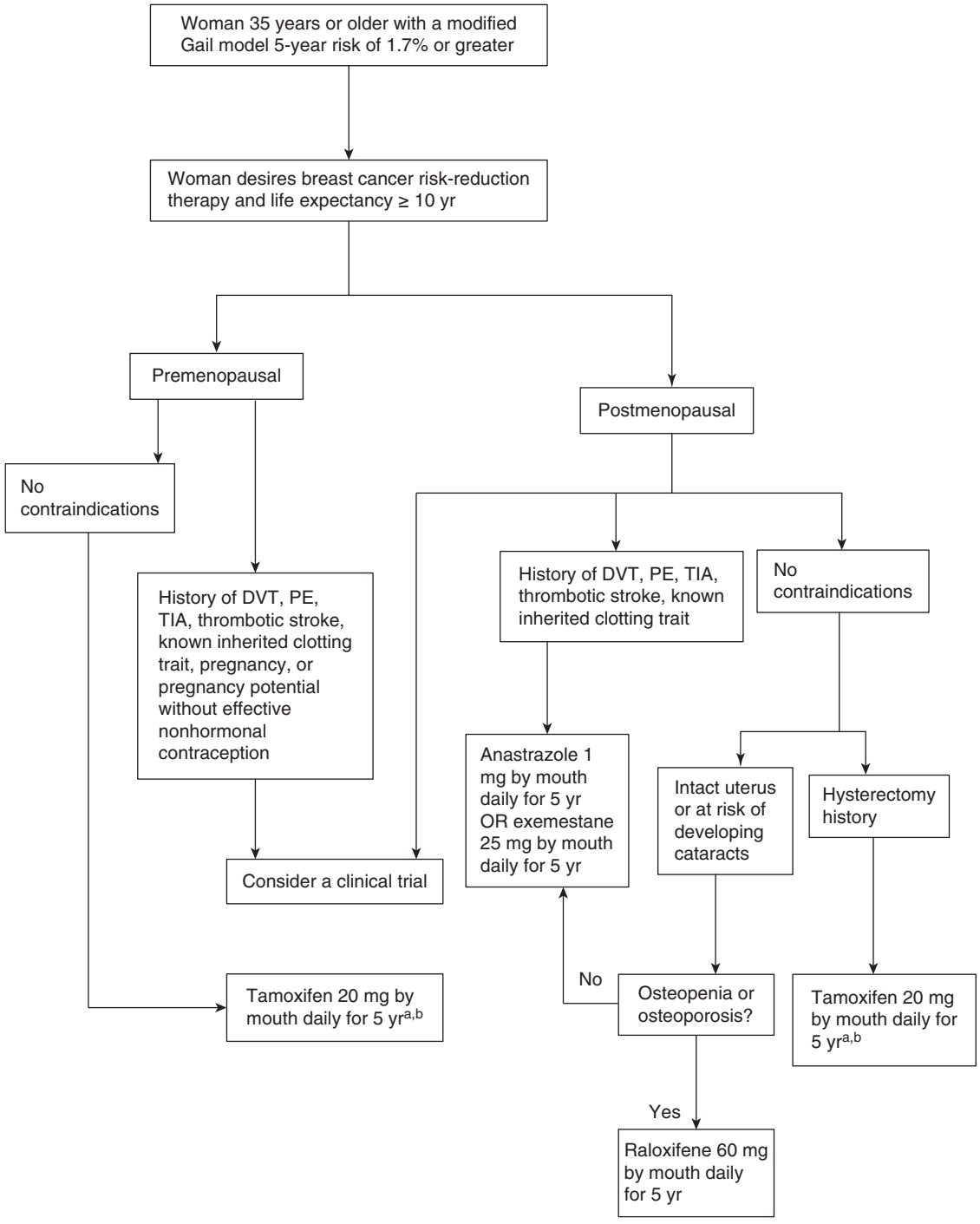

Figure 1-1. Algorithm for the selection of breast cancer risk-reduction treatments.

[a]Review concurrent medications for CYP2D6 inhibitors, which may inhibit tamoxifen metabolism. Consider alternative medications.

[b]May be an option for patients who are carriers of the *BRCA1* or *BRCA2* mutation or who have had prior thoracic irradiation.

[c]Postmenopausal women with no contraindications may receive therapy with tamoxifen, raloxifene, or an aromatase inhibitor (anastrazole or exemestane). Preference for therapy may depend on medical history, as indicated by algorithm, but these are not contraindications.

DVT = deep venous thromboembolism; PE = pulmonary embolism; TIA = transient ischemic attack.

Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction Screening, version 1. 2016.

low risk of cardiovascular disorders, the U.S. Preventive Services Task Force (USPSTF) has concluded that the potential harms associated with NSAID use (other than aspirin) outweigh the benefits for prevention of CRC in the general population (USPSTF 2016). New USPSTF guidelines recommend daily low-dose aspirin (75–100 mg by mouth daily or 100–325 mg by mouth every other day) for at least 10 years in patients age 50–59 who have a life expectancy of at least 10 years and are not at risk of bleeding for primary prevention of cardiovascular disease and CRC. Adults age 60–69 may also receive low-dose daily aspirin for at least 10 years if the benefits outweigh the risks. The greatest benefit of low-dose aspirin in adults age 50–59 is when the 10-year cardiovascular disease risk is 10% or greater. Older adults may also benefit, although the net benefit is smaller because of the increased risk of GI bleeding and the decrease in CRC prevention. The 10-year cardiovascular risk can be calculated using the online risk calculator.

No other guidelines recommend aspirin use for primary prevention of CRC in average-risk adults. Both the American Gastroenterological Association and the NCCN limit their recommendation to patients at increased risk of CRC (Chubak 2015).

Hormone Replacement Therapy

Exogenous postmenopausal oral hormone replacement therapy (estrogen, progesterone, or the combination) is associated with a significant reduction in CRC risk, which persists for about 10 years after therapy is discontinued (Teixeira 2014). However, because postmenopausal hormone replacement therapy increases breast cancer risk and harmful cardiovascular effects, its use is not recommended to prevent CRC.

Polyp Removal

A history of high-risk adenomatous polyps, particularly multiple adenomas or those 10 mm or greater, is associated with an increased risk of CRC (NCCN 2015a). Colonoscopic polypectomy done during a screening colonoscopy is considered the standard of care for all individuals to prevent the progression of premalignant adenomatous polyps to colon cancer lesions. Although no randomized trials show that colonoscopy decreases CRC mortality, results of observational studies not only show a 56%–77% decrease in the incidence in CRC with colonoscopy and polyp removal but also about a 50% reduction in CRC mortality (NCCN 2015a). Therefore, one of the best prevention strategies for CRC is to remove any polyps that are found during colonoscopy. As discussed in the colorectal cancer section that follows, colonoscopy is the gold standard screening measure because it allows for immediate identification and removal of polyps.

HPV-Related Cancers

Human papillomavirus is responsible for almost all (99.7%) cervical cancers (Bailey 2016). Human papillomavirus–related cancers affect both men and women, with HPV causing 60% of oropharyngeal cancers, 63% of penile cancers, 69% of vulvar cancers, 75% of vaginal cancers, and 91% of anal cancers. The most common HPV genotype responsible for these cancers is 16, but several other HPV genotypes (6, 11, 18, 31, 33, 45, 52, and 58) have been associated with cancer as well. Human papillomavirus–related cancers appear to occur disproportionately in health-disparate groups (lower income, lower educational attainment). This may be because of low screening and treatment rates and higher behavioral risk factors, such as early age of first sexual activity.

HPV Vaccines

Three HPV vaccines on the market are effective in preventing many cancers related to HPV (Bailey 2016), including most anal, cervical, penile, vaginal, and vulvar cancers caused by HPV. Although it is known that HPV causes some forms of oropharyngeal cancer, the effectiveness of the HPV vaccine in this setting is unknown. Table 1-1 summarizes the properties, effectiveness, and recommendations for using HPV for cancer prevention. All three of these vaccines are administered as a 3-injection series: initially and 1–2 months and 6 months after initial injection. Ongoing studies are evaluating the possibility of a 1- or 2-injection series in hopes of gaining better compliance with guidelines without compromising efficacy. The current CDC Advisory Committee on Immunization Practices guidelines recommend that girls and boys age 11–12 years (but as early as 9 years) receive HPV vaccination (CDC 2016). Men age 22–26 if they have sex with men or females and men age 22–26 who are immunocompromised should also receive the 3-injection vaccine series. Currently, compliance with CDC Advisory Committee on Immunization Practices guideline recommendations is about 30% (Hopkins 2013). Barriers to vaccination include patient factors (e.g., lack of education and/or discomfort about sexual behavior discussions) and system factors (e.g., reimbursement, reminders about timing of vaccines).

Ovarian Cancer

The association between oral contraceptive use and decreased ovarian cancer risk has been studied in many trials and epidemiologic studies. A potential mechanism for the benefit is that taking oral contraceptives can lead to anovulation. The lack of ovulation leads to less repeated trauma to the ovarian epithelium, which causes a decreased cancer risk. Two large studies support the use of oral contraceptives in decreasing the risk of ovarian cancer (Faber 2013; Vessey 2013). The final results of a cohort study of over 17,000 women in England and Scotland showed that using oral contraceptives decreased the relative risk of developing ovarian cancer by 50% (95% CI, 0.4–0.7) (Vessey 2013). This study included women mainly taking oral contraceptives containing 50 mcg of estrogen or more, which is higher than today's standard oral contraceptives, but showed that the decreased

Table 1-1. Currently Available HPV Vaccines[a]

HPV Vaccine Type	Bivalent	Quadrivalent	9-Valent
Trade name (Manufacturer)	Cervarix (GlaxoSmithKline)	Gardasil (Merck)	Gardasil 9 (Merck)
HPV genotypes	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Effectiveness	Protects against anal (78% men), anal or cervical (96% women), penile (100%), vaginal (100%), vulvar (100%), and genital warts (99% females, 91% males) caused by these genotypes 5-year protection, ongoing study evaluating full effect		Protects against anal (75%, men), anal or cervical (96% women), penile (100%), vaginal (100%), vulvar (100%), and genital warts (99% females, 89% males) caused by these genotypes
CDC ACIP guidelines	Girls age 11–12 years (but as young as 9 years[b]) receive any of these HPV vaccines Boys age 11–12 years (but as young as 9 years[b]) receive only 4- or 9-valent HPV vaccine Men age 22–26 if they have sex with men or women or males who are immunocompromised should receive the 3-injection series		

[a]All HPV vaccines administered as 3-injection series: initial and 1–2 months, and 6 months after initial injection. A catch-up schedule is provided in the guidelines.

[b]May be initiated in children as young as 9 years, particularly in those with history of sexual abuse or assault.

ACIP = Advisory Committee on Immunization Practices; HPV = human papillomavirus.

Information from: CDC. Immunization Schedules [homepage on the Internet].

risk of ovarian cancer continued the longer the patients were on active therapy. In another population-based case-control study, the decrease in risk occurred regardless of the amount of estrogen and progesterone and did not depend on whether the contraceptives were combined hormone therapy or progestin only (Faber 2013). The results of this study show that use of combined oral contraceptives is associated with a statistically significantly decreased risk of ovarian cancer (OR 0.68; 95% CI, 0.53–0.88) and that mixed use of combined and progestin-only pills decreases the risk (OR 0.50; 95% CI, 0.28–0.87). Although these studies report a decreased risk, no current guidelines recommend that all childbearing women use oral contraceptives. Risks (thromboembolism, breast cancer risk with duration > 5 years, continued ovarian cancer screening in women at high risk [e.g., *BRAC1* or *2* mutation]) and benefits should still be considered for each individual woman.

Patients with the *BRCA1* and/or *BRCA2* mutation are also at a high risk of developing ovarian cancer. As discussed in the Cancer Prevention: Breast Cancer section, bilateral salpingo-oophorectomy reduces the risk of ovarian and fallopian tube cancer in women with the *BRCA1* and/or *BRCA2* mutation by about 80% (NCCN 2017). Although chemoprevention with SERMs may help reduce invasive breast cancer in these women, it is not protective against ovarian cancer. Ovarian cancer screening with ultrasonography and CA-125 concentrations is not considered routinely recommended but is advocated by some.

Prostate Cancer

Most prostate cancers occur after age 40, and lifelong exposure to testosterone is thought to be the likely causative factor. Therefore, the use of agents to reduce testosterone concentrations could be effective in preventing prostate cancer.

5-α-Reductase Inhibitors

The enzyme 5-α-reductase converts testosterone to its more active form, dihydrotestosterone, which is responsible for prostate epithelial cell proliferation (Thompson 2003). In fact, continuous use of the 5-α-reductase inhibitors finasteride and dutasteride lowers prostate-specific antigen (PSA) concentrations by as much as 50% after 6 months (NCCN 2016b). Two clinical trials have evaluated these drugs for prostate cancer prevention. The Prostate Cancer Prevention Trial (PCPT) compared finasteride 5 mg orally daily with placebo for 7 years in 18,882 men 55 and older with a normal digital rectal examination (DRE) and a PSA concentration less than 3 ng/mL (Thompson 2003). The trial results showed that finasteride reduced the incidence of prostate cancer by 30% (10.5% vs. 14.9%; RR 0.70; 95% CI, 0.65–0.76, p<0.001). The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial evaluated dutasteride 0.5 mg by mouth daily versus placebo for 4 years in 6729 men age 50–75 with a normal DRE and a PSA concentration of 2.5–10 ng/mL and one negative prostate cancer biopsy within

6 months of enrollment. Similar to the PCPT study, dutasteride significantly reduced the incidence of prostate cancer with a relative risk reduction of 22.8% (95% CI, 15.2–20.8; p<0.001) (Andriole 2010). However, in both studies, the number of men who died of prostate cancer was similar (Thompson 2013; Andriole 2010; Thompson 2003). Furthermore, men receiving 5-α-reductase inhibitor chemoprevention in these trials who later developed prostate cancer tended to have higher-grade tumors (i.e., Gleason score 7–10), and sexual dysfunction adverse effects were commonly reported. Thus, according to these study results, the FDA Oncologic Drugs Advisory Committee did not recommend either agent for chemoprevention, and these agents are not routinely used for prostate cancer prevention. Of note, a long-term follow-up (18 years) analysis of the PCPT study results showed that although more men did develop high-grade tumors, no increase in cancer mortality occurred in these men as might be expected. Thus, the incidence of high-grade tumors after finasteride therapy may not be from promotion of aggressive tumor development but from an artifact of finasteride therapy (Thompson 2013). Several ongoing trials are evaluating other chemoprevention agents that are focused on dietary supplements (e.g., lycopene).

CANCER SCREENING

Several organizations provide guideline recommendations for cancer screening. Recommendations vary on which cancers people should have screening tests for, which screening tests should be used to screen for a particular cancer, and when and how often those screening tests should be done. Recommendations for routine cancer screening are available for breast, cervical, colorectal, lung, and prostate cancers. In addition, guidance on endometrial and skin cancers will be discussed. Three organizations provide screening guidelines for each of these cancers: the American Cancer Society (ACS), NCCN, and USPSTF. In addition, professional organizations specific to the disease state (e.g., American Congress of Obstetricians and Gynecologists [ACOG] for breast cancer screening) may provide guidelines. Often, guidelines from various organizations have similar recommendations for the types of screening tests to use but different recommendations for the frequency of screening, when to start screening, and when to end screening. The NCCN screening guidelines are updated at least annually; the other guidelines are updated less often.

Individuals known to be at a high risk of cancer, such as those with a personal history of cancer or a strong family history of cancer (in two or more first-degree relatives), may require a different type, frequency, and initial timing of screening. The subsequent sections will discuss screening recommendations for normal- and high-risk patients.

Breast Cancer

Types of Screening Methods

The type of screening used for breast cancer depends on the patient's risk factors and may include breast cancer awareness, clinical breast examination (CBE), risk assessment, mammography, and, in some cases, breast MRI. Of importance, a diagnostic breast evaluation (one that evaluates an existing problem) differs from a breast screening. For example, a breast ultrasound may be used in a diagnostic workup of women who may have a lump and/or positive findings on other screening tests, but this is not part of routine screening.

A CBE includes an inspection of the breast by a health care provider in both the upright and supine positions, to detect any subtle shape or contour changes in the breast (NCCN 2015b). In addition, women should become familiar with their own breasts and promptly report any changes to their health care provider. Breast self-examination may be useful for patients to do to maintain consistent breast awareness. Risk assessment categorizing the patient into normal and high risk is important because screening recommendations differ for these two groups. High-risk patients include those with an increased lifetime risk according to models or a genetic predisposition to cancer. More details are provided in screening guidelines for high-risk patients (in the Screening Guidelines section that follows). Mammography screening involves two radiographic images of each breast: one taken from the top of the breast and one from the side of the breast. Mammography has a 75% sensitivity rate overall, but it decreases in women with dense breasts (50%) and those with a known *BRCA1* and/or *BRCA2* mutation (33%) (Berg 2008; Kuhl 2005; Carney 2003). Breast MRI screening uses a powerful magnetic field, radiofrequency pulses, and a computer to create detailed pictures of the breasts. Although the sensitivity is much higher with breast MRI (94%–100%), the specificity is lower (37%–97%), making it much more likely to cause false-positive results (Orel 2000; Orel 1994).

Screening Guidelines for Normal-Risk Patients

Each of the guidelines recommends regular breast self-examination, and the ACOG and NCCN recommend a routine CBE every 1–3 years at age 25–40 and yearly after age 40 (ACOG 2016; Sui 2016; NCCN Breast Cancer Screening 2015; Oeffinger 2015). The NCCN recently changed its CBE to include not only a CBE but also ongoing risk assessment and risk reduction counseling, if appropriate, and redefined it as a clinical encounter. Breast MRI is not recommended for normal-risk patients (ACOG 2016; NCCN Breast Cancer Screening 2015). Although all of the guidelines recommend mammography for breast cancer screening, controversy exists on its benefit, particularly in younger women. Some data suggest that mammography leads to the overdiagnosis of breast cancer, only modestly reducing the risk of breast

Table 1-2. Mammography Breast Cancer-Screening Guidelines for Normal-Risk Patients

Guideline (Year Updated)	When to Begin Screening	When to Stop Screening	Testing Frequency
American Cancer Society (2015)	Age 45[a]	Life expectancy < 10 years	Yearly until age 54, then every 2 years
American Congress of Obstetricians and Gynecologists (2011; reaffirmed 2014)	Age 40	Reevaluate life expectancy at age 75	Yearly
National Comprehensive Cancer Network (2016)	Age 40	If treatment would not occur	Yearly[b]
U.S. Preventive Services Task Force (2016)	Age 50[a]	Age 75	Every 2 years

[a]May begin at age 40.

[b]Digital tomosynthesis may be used instead of traditional mammography.

Information from: Oeffinger KC. Breast cancer screening for women at average risk. 2015 guideline update from the American Cancer Society. JAMA 2015;314:15:1599-614; American Congress of Obstetricians and Gynecologists Practice Bulletin 2011; 122:1-11; National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, version 1, 2015; Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer. U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164:279-96.

cancer mortality (Siu 2010). Therefore, the recommendations differ regarding the timing to begin breast cancer screening and the frequency of screening tests. Over the past 15 years, the timing of breast cancer screening has changed from beginning annual screening at age 40 to starting screening at age 40–50 annually to every other year (because relative benefits of annual screening as a woman ages after menopause decreases), depending on the guideline. Breast cancer screening should stop when the patient has a life expectancy of less than 10 years or age 75. In addition, the NCCN now recommends consideration of tomosynthesis (i.e., three-dimensional radiography) as an alternative to mammography. Table 1-2 provides the most current recommendations for breast cancer screening in normal-risk patients.

Screening Guidelines for High-Risk Patients

Both the ACS and the NCCN offer guideline recommendations for patients at a high risk of developing breast cancer (ACS 2016b; NCCN Breast Cancer Screening 2015). The ACS identifies high-risk patients as women with a breast cancer lifetime risk of 20%–25% and one of the following: (1) *BRCA1* or *BRCA2* gene mutation or first-degree relative with gene mutation but patient has not been tested yet; (2) therapeutic thoracic radiation therapy at age 10–30 years; or (3) Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome in themselves or a first-degree relative. These high-risk patients should receive annual breast MRI and mammography screening (ACS 2016b). The NCCN recommends a mammography, CBE, and consideration of breast MRI and prevention strategies for patients at high risk (NCCN 2015b). Those at high risk within this guideline include (1) women 35 and older with a 5-year risk of invasive breast cancer of 1.7% or greater by the Gail model; (2) women with a lifetime risk of breast cancer of greater than 20% according to family history models; (3) women who have previously received therapeutic thoracic radiation therapy; (4) women with LCIS and atypical ductal or lobular carcinoma; and (5) women with a family history suggestive of genetic predisposition. Specific NCCN screening recommendations, frequency, and time to initiate screening for these patients are listed in Table 1-3.

Cervical Cancer

Before cervical cancer screening began, cervical cancer was one of the most common causes of death in women. The reduction in mortality through cervical cancer screening has occurred by detecting precancerous lesions as well as invasive cancer at early stages, thereby increasing the overall survival rate of cervical cancer to about 92% (Saslow 2012).

Types of Screening Methods

Cervical cancer screening is recommended for women from age 21 to about age 65 to reduce the morbidity and mortality from cervical cancer. Two screening methods are used: cervical cytology and HPV testing. Two methods are available for preparing a specimen for cervical cytology: the conventional Papanicolaou (Pap) smear and liquid-based cytology. Both methods use cells obtained from the external surface of the cervix and the cervical canal using a spatula and/or brush. The Pap smear is a collection of cells on a microscope slide that is examined by a pathologist under

Table 1-3. Breast Cancer-Screening Guidelines for High-Risk Patients[a]

High-Risk Feature	Screening Test	When to Begin Screening	Testing Frequency
BRCA1 or *BRCA2* mutation	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 25	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 25–29	Yearly
	Mammography and breast MRI with contrast	Age 30–75[c]	Yearly
Li-Fraumeni syndrome	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 20–25	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 25–29	Yearly
	Mammography and breast MRI with contrast	Age 30–75[c]	Yearly
Cowden syndrome/PHTS	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 25 or 5–10 years before earliest known breast cancer in family	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 30–35 or 5–10 years before earliest known breast cancer in family[c]	Yearly
Women ≥ 35 with a 5-year Gail model risk of 1.7% or higher	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age identified as being at increased risk by Gail model	Every 6–12 months
	Mammography (consider tomosynthesis)	Age identified as being at increased risk by Gail model	Yearly
		If treatment would not occur	Yearly
Women with a lifetime risk > 20% because of LCIS or ADH/ALH	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	At diagnosis of LCIS or ADH/ALH	Every 6–12 months
	Mammography (consider tomosynthesis)	At diagnosis of LCIS or ADH/ALH but before age 30	Yearly
	Consider MRI	At diagnosis of LCIS or ADH/ALH but not before age 25	Yearly
Women with lifetime risk > 20% on family history risk models	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b,d])	Age identified as being at increased risk	Every 6–12 months
	Mammography (consider tomosynthesis)	Beginning 10 years before youngest family member but not before age 30	Yearly
	Consider MRI	Beginning 10 years before youngest family member but not before age 25	Yearly

Prior thoracic radiation therapy at age 10–30 years and current age ≥ 25	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE)	Beginning 8–10 years after radiation therapy	Every 6–12 months[e]
	Mammography (consider tomosynthesis)	Beginning 8–10 years after radiation therapy but not before age 25	Yearly
	Consider MRI	Beginning 8–10 years after radiation therapy but not before age 25	Yearly

[a]All patients should be familiar with breast awareness and should promptly report any changes.
[b]Consider risk reduction strategies
[c]Age > 75, individualize screening.
[d]Refer for genetic counseling.
[e]If current age ≤ 25, perform yearly.
ADH = atypical ductal hyperplasia; ALH = atypical lobular carcinoma; CBE = clinical breast examination; LCIS = lobular carcinoma in situ; PTHS, phosphatase and tensin homolog (*PTEN*) Hamartoma tumor syndrome.
Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, version 1. 2015; and National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer, version 1. 2017.

a microscope, whereas liquid-based cytology is a collection of cells placed in a vial containing a liquid medium that is processed by a laboratory into a cell thin layer, stained, and examined by light microscopy. These methods are thought to be equivalent in detecting positive findings, according to two randomized trials (Moyer 2012a). Human papillomavirus testing is also done by collecting cells from the endocervix by a spatula or brush. One of the available HPV tests detects the presence or absence of high-risk HPV types (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 68, 69, 82), whereas the other tests report the presence or absence of HPV 16 and 18, which are associated with high-grade cancers. No specific HPV test is recommended by the guideline, but the test should conform to current standards for well-validated HPV DNA tests (Saslow 2012).

Screening Guidelines for Normal-Risk Patients

The ACS, American Society of Colposcopy and Cervical Pathology, American Society for Clinical Pathology, USPSTF, and ACOG have published guidelines for cervical cancer screening (ACOG 2016; Moyer 2012a; Saslow 2012). Each of these guidelines recommends that cervical cancer screening begin at age 21, with cervical cytology (e.g., Pap smear) every 3 years. When women reach age 30, they may wish to lengthen the screening interval and thus may have cervical cytology and HPV testing, often called "co-testing," every 5 years. At age 65, if the woman has no history of moderate or severe cervical dysplasia or cancer, has had three consecutive negative Pap smears or two consecutive co-test results within the past 10 years, and has had cervical cancer screening within the past 5 years, she may stop screening. Women who have had a hysterectomy with removal of the cervix and no history of high-grade cancerous lesions no longer need to have cervical cancer screening. However, if the hysterectomy does not remove the entire cervix or the patient has a history of high-grade precancerous lesions, continued cervical cancer screening should occur. Prior HPV vaccination does not change the recommendations for cervical cancer screening because the vaccine is not completely effective in preventing cervical cancer. Controversy exists over continuing annual pelvic examinations. In 2014, the American College of Physicians (ACP) released guidelines recommending against annual pelvic examinations in healthy, low-risk women because these women do not meet the criteria for effective screening procedures (Qassem 2014). However, the ACOG recommends annual pelvic examinations with a speculum and bimanual examinations for women older than 21 because they not only assist in identifying malignancies, but may also assist in recognizing incontinence and sexual dysfunction (Burns 2015).

Screening Guidelines for High-Risk Patients

Patients at a high risk of developing cervical cancer need more intensive or alternative screening. These include women with a history of precancerous cervical cancer, those with in utero exposure to diethylstilbestrol, and those who are immunocompromised (e.g., HIV, or long-term corticosteroid use) (Saslow 2012). The optimal screening tests and frequency in these populations are unknown, and existing guidelines do not specifically address all high-risk populations. Women with a history of precancerous lesions should initially have cervical cytology and HPV co-testing 12 and

24 months after treatment. If both tests are negative, co-testing should be repeated in 3 years; then, if negative again, the patient can begin regular cervical screening recommendations for normal-risk patients for a minimum of 20 years, even if this extends beyond age 65 (Massad 2013). Daughters of women exposed to diethylstilbestrol should have annual screening that continues until they are no longer a candidate for treatment if cervical cancer is diagnosed, such as if they have comorbidities that preclude the safe administration of treatment. The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents recommends that patients with HIV begin screening at the time of sexual activity but no later than age 21 and continue throughout the woman's life (Panel on Opportunistic Infections 2015). Annual screening with cervical cytology is recommended in women younger than 30; once they have three consecutive negative tests, the screening interval can be extended to every 3 years. Women with HIV-positive infection who are 30 and older can be screened with cervical cytology or co-testing annually. Again, if three consecutive negative tests occur, the screening interval can be extended to 3 years. Women with other immunocompromised diseases are advised to follow these recommendations because no specific studies or society recommendations exist.

Colorectal Cancer

Patients with localized CRC have a 91% 5-year survival rate, whereas those with advanced or distant disease have a 72% 5-year survival rate, showing that an earlier diagnosis can affect survival (NCCN 2015a). Furthermore, 63% of CRC deaths are attributed to non-screening.

Types of Screening Methods

Colorectal cancer screening can be completed using structural or fecal-based tests. Structural tests can detect both early cancer and polyps using either endoscopic imaging (i.e., colonoscopy, flexible sigmoidoscopy) or radiologic imaging (i.e., virtual colonoscopy, flexible sigmoidoscopy, CT colonography). Colonoscopy uses an endoscope to fully examine the entire large bowel, including the cecum in most patients, and allows for simultaneous removal of premalignant lesions (i.e., polyps). Flexible sigmoidoscopy uses a 60-cm flexible sigmoidoscope to examine the lower half of the bowel to the splenic flexure for most patients. The CT colonography or virtual colonoscopy is an imaging procedure that creates two- and three-dimensional images of the colon using CT scans. Lesions suggestive of cancer found during CT colonography or flexible sigmoidoscopy require further evaluation/removal by colonoscopy. Therefore, colonoscopy is considered the gold standard for CRC screening.

Fecal tests detect signs of CRC in stool samples: occult blood (i.e., fecal occult blood tests) or alterations in exfoliated DNA (i.e., stool DNA test) that may be associated with bleeding adenomas or cancer. Guaiac-based fecal occult blood tests (gFOBTs) detect peroxidase activity of heme when hemoglobin comes in contact with a guaiac-impregnated paper (Levin 2008). Typically, the patient will require three consecutive bowel movement samples with gFOBT (Box 1-2). A small amount of feces is smeared on the kit's paper and covered with the provided kit. When hydrogen peroxide is dropped onto the paper with feces, a blue color appears if trace amounts of blood are present. False-negative and false-positive results can occur with certain diets and medications (Box 2).

Fecal immunochemistry tests (FITs) were developed to reduce false-negative and false-positive results associated with gFOBT. These tests use antibodies to detect globulin protein in hemoglobin when it is present in stool. Because globulin is degraded by enzymes in the upper GI tract, it is more specific for lower GI bleeding. The patient collects a small amount of feces using a probe provided in the kit and mails it to a laboratory for processing. Unlike gFOBT, the FIT does not require dietary restrictions and only requires a single stool sample annually.

DNA screening tests use molecular-screening strategies to detect elevated concentrations of altered DNA and/or hemoglobin, which may be present in feces. As in the FIT test, the patient collects a small amount of feces using a probe

Box 1-2. Causes of False-Negative or False-Positive Guaiac-Based Fecal Occult Test Results

False Positives

Dietary

- Consumption of red meat (beef, lamb, liver) and raw vegetables with peroxidase activity (turnips, broccoli, cauliflower, and radishes) within 3 days before testing[a]

Medical

- Rectal enemas, rectal medications, and digital rectal examination within 3 days before testing
- Aspirin or NSAIDs within 7 days before testing
- Testing if blood from hemorrhoids is present in stool
- Testing if within 3 days of menstrual activity

False Negatives

Dietary

- Consumption of vitamin C in excess of 250-mg supplements or from citrus fruits or juices within 3 days before testing

Medical

- Testing dehydrated samples

[a]Test instructions for several products no longer contain dietary vegetable or fruit restrictions.

Information from: Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008; a joint guideline from the American Cancer Society, the US Multi-Society on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:138-60.

provided in the kit and sends a full bowel movement sample to a laboratory for processing. Like FIT, DNA screening also does not require dietary restrictions and requires only a single stool sample. However, the optimal interval for screening is unknown at this time. Benefits and limitations of each screening method are described in Table 1-4.

Screening Guidelines for Normal-Risk Patients

Men and women 50 and older with no history of adenomas, polyps, or inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease) and no family history (e.g., none or only distant relatives) of CRC are considered at an average risk of developing CRC (NCCN 2015a). The ACS, NCCN, USPSTF, and

Table 1-4. Benefits and Limitations of Available CRC Screening Methods

Screening Method	Benefits	Limitations
Structural Examinations		
Colonoscopy	• View entire colon • Most sensitive screening method • Can remove polyps • Few complications	• Full bowel preparation required • Can be expensive • Sedation and chaperone required • Highest bowel tear/perforation rate • Requires missed day of work
CT colonography	• Examines entire colon • High sensitivity and specificity for moderate-large adenomas • Fairly quick • Few complications • No sedation needed • Noninvasive	• Full bowel preparation required • Cannot remove polyps • Low-dose radiation exposure • Colonoscopy required if abnormalities • Not covered by all insurers
Flexible sigmoidoscopy	• Few complications • No sedation needed	• Views only one-third of colon • Cannot remove large polyps • Small risk of infection or perforation • Slightly more effective than FOBT at detecting CRC • Colonoscopy required if abnormalities • Limited availability
Fecal Tests		
DNA test	• No bowel preparation needed • Sampling done at home • Requires only a single stool sample • No sedation needed • Noninvasive	• Will miss most polyps • High cost compared with other fecal tests • New technology with uncertain testing interval • Colonoscopy necessary if abnormal
Fecal immunochemistry test (FIT)	• No bowel preparation needed • Sampling done at home • Requires only a single stool sample • Low cost • No sedation needed • Noninvasive	• Will miss most polyps • May produce false-positive results • Slightly more effective at detecting CRC when done in combination with sigmoidoscopy at 5 years • Colonoscopy necessary if abnormal • Requires multiple stool samples
Guaiac-based fecal occult test (FOBT)	• No bowel preparation needed • Sampling done at home • Low cost • No sedation needed • Noninvasive	• Requires pretest dietary and medication limitations • Requires multiple stool samples • Will miss most polyps • May produce false-positive results • Slightly more effective at detecting CRC when done in combination with sigmoidoscopy at 5 years • Colonoscopy necessary if abnormal

CRC = colorectal cancer.

Information from: American Cancer Society (ACS). Colorectal Cancer Facts & Figures 2014–2016. Atlanta: ACS, 2014.

Table 1-5. CRC Screening Recommendations for High-Risk Patients

High-Risk Patient Type	Recommendation
Family History	
One first-degree relative with CRC diagnosed before age 60 or two first-degree relatives with CRC diagnosed at any age	Begin CRC screening with colonoscopy every 5 years beginning 10 years before the earliest family member's diagnosis age or at age 40 at the latest
One first-degree relative with CRC diagnosed at age 60 and older or one second-degree relative with CRC diagnosis at younger than 50	Begin CRC screening with colonoscopy at age 50 but may have screening interval shortened to every 5–10 years
One or more first-degree relative with an advanced adenoma	Begin CRC screening with colonoscopy every 5–10 years at age of onset of advanced adenomas diagnosis in their relative or at age 50 at the last test
Personal History	
Inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis)	Begin CRC screening using a colonoscopy every 1–2 years 8–10 years after symptom onset
High-risk familial syndromes (e.g., Lynch, polyposis, Cowden, and Li-Fraumeni syndromes)	Refer for genetics counseling at a cancer center that is well equipped to handle appropriate screening, diagnosis, and treatment

Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, version 1. 2015.

American College of Gastroenterology all have guideline recommendations for CRC screening (NCCN 2015a; Smith 2015; Rex 2009; USPSTF 2008). Each of these guidelines recommend that beginning at age 50, men and women be screened for CRC. The American College of Gastroenterology suggests that African Americans should begin screening at age 45 (Rex 2009). The only guideline that recommends when to stop screening for CRC is the USPSTF, which recommends against routine screening for patients older than 75 (USPSTF 2008). Each guideline recommends colonoscopy screening every 10 years, gFOBT or FIT annually, or flexible sigmoidoscopy with or without gFOBT (or FIT, according to the ACS and the NCCN) every 5 years. In addition, the ACS recommends a CT colonography every 10 years and stool DNA testing without a recommended frequency (Smith 2015).

Screening Guidelines for High-Risk Patients

Patients with high-risk features include those with a family history of CRC, inflammatory bowel disease, or high-risk syndromes (e.g., Lynch, polyposis, Cowden, and Li-Fraumeni syndromes). The screening guidelines for these patients are more aggressive and are detailed in Table 1-5 (NCCN 2015a).

Lung Cancer

Lung cancer is the leading cause of mortality worldwide (NCCN 2016c), despite having an incidence similar to other common cancers like breast, colorectal, and prostate cancer. This discrepancy has been attributed to the fact that screening programs for these other cancers have been in place for decades. Recommendations for routine screening for lung cancer are relatively new, with the first guidelines introduced in 2011.

Types of Screening Methods

Initial lung cancer-screening trials evaluated the use of chest radiographs to improve lung cancer survival. However, most of these studies had flawed study designs and insufficient power, and none showed a benefit in lung cancer diagnoses or mortality (NCCN 2016c). More recently, studies have evaluated low-dose CT lung cancer screening. Low-dose CT delivers 20% of the radiation dose as conventional CT, yet there is comparable sensitivity and specificity for lung nodule detection with this method (Sharma 2015). The relative risk of lung-cancer mortality significantly decreases (RR, 20%; 95% CI, 6.8-26.7; p=0.004) with the use of low-dose CT screening in patients at risk of lung cancer (NCCN 2016c).

Screening Guidelines for Patients at Risk

The American College of Chest Physicians, ACS, NCCN, and USPSTF provide guidelines on the screening for patients with lung cancer at risk (NCCN 2016c; Moyer 2014; Detterbeck 2013; Wender 2013). These organizations all recommend that patients 55 and older with no signs of lung cancer be assessed for smoking history. Those who have at least a

30 pack-year smoking history, who currently smoke, or who have quit within the past 15 years and are in good health should be considered for lung cancer screening. The NCCN also recommends that patients 50 and older with a 20 pack-year or more history of smoking and one additional risk factor (i.e., occupational exposure to carcinogens, residential radon exposure, history of cancer, family history of lung cancer, and/or history of lung disease) be considered for lung cancer screening (NCCN 2016c).

The decision to screen for lung cancer, however, should be a shared health care provider/patient decision after a discussion of the benefits and risks of screening. Benefits of screening include (1) decreased lung cancer mortality or improvement of other oncologic outcomes; (2) improved quality of life; and (3) detection of other lung diseases that require treatment. Risks of screening include (1) false-positive results leading to unnecessary tests, invasive procedures, cost, and psychological distress; (2) false-negative results, which may delay or prevent diagnosis and treatment; (3) detection of aggressive tumors that do not alter overall survival; (4) overdiagnosis resulting in unnecessary treatment; (5) indeterminate results requiring further testing; (6) radiation exposure; and (7) physical complications from diagnostic workup (NCCN 2016c). If the provider and the patient agree to begin lung cancer screening with annual low-dose CT scans, the decision to stop routine screening differs, depending on the guideline. The exact benefit of lung cancer screening beyond age 75–80 is unknown because the original trials evaluating lung cancer screening only included individuals age 50–70 or 75, depending on the trial. The American College of Chest Physicians, ACS, and NCCN recommend to stop screening at age 75 or if the patient is no longer eligible for lung cancer treatment because of comorbidities/preference (NCCN 2016c; Moyer 2014; Detterbeck 2013; Wender 2013). The USPSTF guidelines recommend to stop screening at age 80 or when a person has not smoked for 15 years (Moyer 2014).

Patient Care Scenario

A 52-year-old woman who recently emigrated from Bolivia is in your primary care clinic for the first time this week. Her medical history is significant for obesity and osteoarthritis. She has a 34 pack-year history of smoking and currently is trying to quit but denies alcohol use. She has no significant family history for cancer. She is single and has no children. You have been charged with developing a cancer-screening plan for this patient.

ANSWER

The first step is to identify the types of cancer screening the patient is eligible for and whether your institution follows specific guidelines for cancer screening. The NCCN has recommendations for each of these cancers that are updated at least annually, whereas other professional societies have guidelines that may be updated less often. The guideline that your institution selects is an individual choice. The most important aspect is to be sure you access the most recent guideline recommendations.

As a woman, this patient is at risk of developing breast, cervical, colorectal, endometrial, lung, ovarian, and skin cancer. To determine the appropriate type of screening, a risk factor assessment will need to be completed for each type of cancer. The patient has no known mutations for *BRCA1* or *BRCA2*, nor does she have a history of therapeutic thoracic radiation therapy or genetic syndrome; thus, she is at an average risk of breast cancer. Screening with mammography is recommended in all of the recommended guidelines for a woman age 52 every 1–2 years (ideally beginning at age 40–50 years, depending on the guideline). Similarly, this patient is at an average risk of developing cervical cancer because she has no precancerous cervical cancer and no exposure in utero to diethylstilbestrol and is not immunocompromised. Therefore, screening with cervical cytology and HPV testing at least every 5 years is recommended. This patient is also at an average risk of developing CRC because she has no family history of CRC, inflammatory bowel disease, or high-risk syndromes. Therefore, CRC screening should begin immediately (age 50, ideally). Selection of CRC screening method may depend on patient and provider preference. The gold standard screening method is colonoscopy because it can be used to screen for and remove polyps and adenoma (preventing CRC development). If colonoscopy is chosen, it should be done every 10 years. Alternatives include gFOBT and FIT yearly or flexible sigmoidoscopy with or without gFOBT or FIT every 5 years. Because this woman is a smoker, she should be considered for lung cancer using low-dose CT scans annually. Screening guidelines are not currently available for endometrial or ovarian cancer. The patient could be educated about risks and symptoms of endometrial cancer when she goes through menopause and self-skin checks for skin cancer.

1. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;156:880-91.
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, 2015.
3. NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, 2015.
4. NCCN Clinical Practice Guidelines in Oncology. Lung Cancer Screening, 2016.

Prostate Cancer

In 2015, prostate cancer mortality rates were reduced by almost one-half from their highest rates because of early detection through cancer-screening programs and improved treatment (Siegal 2015).

Types of Screening Methods

Prostate-specific antigen is a glycoprotein that is secreted by prostatic epithelial cells and that enhances sperm motility. It can enter the bloodstream; the normal range is 4–10 ng/mL (NCCN 2016b). Prostate-specific antigen is not a prostate cancer–specific marker, and elevated concentrations may be caused by benign prostatic hyperplasia, prostatitis, or instrumentation of the prostate. However, PSA is used for prostate cancer screening because screening has survival benefits. At a PSA cutoff of 3.1 ng/mL, PSA has a sensitivity of 32% and a specificity of 87% (Thompson 2013). The PSA concentrations can be elevated because of infection, recent instrumentation, ejaculation, or trauma (NCCN 2016b). Conversely, 5-α-reductase inhibitors (e.g., dutasteride, finasteride), when used to treat benign prostatic hyperplasia, and ketoconazole, which inhibits androgen synthesis, can decrease PSA concentrations. Herbal supplements such as saw palmetto can affect PSA, but little is known about the exact effects. Therefore, it is always recommended to obtain a thorough medication history when evaluating PSA concentrations.

Digital rectal examination is a manual examination technique in which the health care provider inserts a gloved finger into the rectum and then palpates the prostate through the rectal wall. Prostate gland size, shape and consistency, and mobility can be noted during a DRE. The positive predictive value of this examination is poor (4%–11%); therefore, as a solo screening test, it is not recommended (Schröder 1998; Flanigan 1994). If a DRE is used, it should be combined with PSA testing.

Screening Guidelines for Normal-Risk Patients

The ACS, American Urology Association (AUA), ACP, NCCN, and USPSTF all have guidelines for prostate cancer screening (Carter 2016; NCCN Prostate Cancer Early Detection 2016; Qaseem 2013; Wolf 2010). Each of these societies, except for the USPSTF, recommends beginning a conversation about the risks and benefits of prostate cancer screening in men at age 45 (NCCN), 50 (ACP and ACS), or 55 (AUA) (Carter 2016; NCCN Prostate Cancer Early Detection 2016; Qaseem 2013; Wolf 2010). The USPSTF recommends against PSA-based routine screening in men without symptoms because the reduction in prostate cancer mortality is very small and the harms of screening (pain, fever, infection, transient urinary difficulties associated with prostate biopsy) and prostate cancer treatment (e.g., erectile dysfunction, urinary incontinence, bowel dysfunction, premature death) may outweigh the benefit of detecting prostate cancer in asymptomatic men (Moyer 2012b). The ACP, ACS, AUA, and NCCN recommend PSA testing. The NCCN also recommends considering a baseline DRE. The frequency of testing depends on the guidelines, but essentially, all recommend repeating PSA every 1–4 years, depending on PSA concentration, and screening should not continue in patients with a life expectancy of less than 10–15 years (or typically around age 70–75 for most men) (Table 1-6).

Table 1-6. Prostate Cancer-Screening Guidelines

Organization	Initiation	Cessation	Frequency
American Cancer Society	Age 50 with life expectancy > 10 years	Asymptomatic with life expectancy < 10 years	Every 1–2 years, depending on PSA concentration
American College of Physicians	Age 50	Age 70 with life expectancy < 10–15 years	Every 1–4 years; every year if PSA ≥ 2.5 ng/mL
American Urological Association	Age 55	Age 70 or men with life expectancy < 10–15 years	Every 2 years or more, if preferred
National Comprehensive Cancer Network	Age 45	Age 75; may continue in select patients	Every 1–4 years, depending on PSA concentration
U.S. Preventive Services Task Force	Recommends against PSA-based screening for men without symptoms		

PSA = prostate-specific antigen.

Information from: Qaseem A, Berrty MJ, Denberg TD, et al. Screening for prostate cancer: a guidance statement from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2013;158:761-9; Carter HB, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. American Urological Association, 2016; National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate Cancer Screening, 2016; Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157:120-34; and Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer; Update 2010. CA Cancer J Clin 2010;60:70-98.

Screening Guidelines for High-Risk Patients

African American men with a first-degree relative with prostate cancer, particularly when it is diagnosed at a younger age, are at a higher risk of prostate cancer (about 2-fold) (NCCN 2016b). Several organizations, including ACP, ACS, and AUA, recommend that high-risk patients begin prostate cancer screening at age 40–45 (Carter 2016; Qaseem 2013; Wolf 2010). Other organizations, such as the USPSTF and NCCN, however, do not recommend different screening guidelines for high-risk patients (NCCN 2016b; Moyer 2012). This is because the effects of earlier treatment or more intensive screening in these patients are not apparent. The large prostate cancer-screening trials that showed the benefit of screening often either had small populations of high-risk patients (e.g., Prostate, Lung, Colorectal and Ovarian Trial, 4.4% African Americans; 6.9% of the patients enrolled had a positive family history) or no data on race or family history. Therefore, the NCCN panel currently states that evidence is insufficient to recommend different screening recommendations, but these individuals should be monitored closely for adherence to screening. Thus, patients with a high-risk feature, such as African American race or family history, should engage in a thorough discussion with their health care providers about the risks and benefits of beginning prostate cancer screening earlier than age 45.

Practice Points

- **Cancer prevention and screening can prevent many cancers and detect precancerous or early-stage cancers, significantly reducing morbidity and mortality. Developing an appropriate cancer screening and, if appropriate, prevention plan, should be part of routine preventive care medicine.**
- **Cancer prevention strategies are available for women who have the *BRCA1* and/or *BRCA2* mutation or other high-risk features.**
- **Low-dose aspirin (75–100 mg by mouth daily or 100–325 mg by mouth every other day) is recommended for adults age 50–59 with a life expectancy of at least 10 years and not at risk of bleeding to prevent CRC; adults age 60–69 may also benefit.**
- **Polyps should be removed, when detected, to prevent CRC development.**
- **The HPV vaccine should be administered to boys and girls, men age 22–26 who have sex with men, and adults age 22–26 who are immunocompromised, to prevent HPV-related cancers, according to the 2016 CDC Advisory Committee on Immunization Practices guidelines.**
- **Routine cancer-screening recommendations are available for breast, cervical, CRC, lung, and prostate cancer in both patients at average risk and those at high risk.**
- **Guidelines may differ in their recommendations, and the most recent guidelines should be consulted when developing a patient-specific cancer-screening plan.**

Other Cancer Screening

Endometrial Cancer Screening for High-Risk Patients

Currently, no screening tests are available for endometrial cancer. The ACS, however, does recommend that when a woman undergoes menopause, she be educated about the risks and symptoms of endometrial cancer and immediately report any vaginal bleeding, discharge, or spotting (Smith 2001). In addition, women at an increased risk of endometrial cancer, including those who have never given birth; have infertility, diabetes, or hypertension; or have taken estrogen or tamoxifen therapy, should be educated on reporting abnormal vaginal bleeding promptly. Moreover, women with hereditary nonpolyposis colon cancer (often called Lynch syndrome) are at a high risk of endometrial cancer. These women should receive an annual endometrial biopsy beginning at age 35.

Skin Cancer-Screening Recommendations

Skin cancer is the most commonly diagnosed cancer in the United States. In the past, it was recommended that health care providers regularly perform a full-body skin examination. Despite this, randomized clinical trials have not examined whether screening improves outcomes such as reduced morbidity and mortality of skin cancer (USPSTF 2009). Therefore, the USPSTF recommends against any routine skin cancer screening. The American Academy of Dermatology promotes skin cancer screening through regular skin self-examinations for all individuals and offers free cancer screenings throughout the year. Patients with a history of skin cancer or melanoma should receive more regular screening by a dermatologist.

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

K.G. is a 58-year-old white man in the clinic for a medication therapy management follow-up visit. His primary care physician has recommended colorectal cancer (CRC) screening, but K.G. recently read a news article about drugs to prevent CRC. K.G. wants your advice about the screening and prevention methods. K.G.'s medical history includes hyperlipidemia, hypertension, and coronary artery disease; he is a nonsmoker. His home drugs include simvastatin 20 mg by mouth at bedtime and hydrochlorothiazide 25 mg by mouth daily. K.G.'s blood pressure today is 158/78 mm Hg, and his fasting lipid panel results are TC 200 mg/dL and HDL 30 mg/dL.

1. Which one of the following best justifies recommending CRC screening in K.G.?

   A. Reduces risk factors.
   B. Identifies cancerous lesions for removal.
   C. Identifies cancers at an early stage.
   D. Alters carcinogenesis.

2. Which one of the following is the best colorectal screening option to recommend for K.G.?

   A. Colonoscopy every 5 years
   B. CT colonography every 5 years
   C. Fecal immunochemistry test (FIT) annually
   D. Guaiac-based fecal occult blood test (gFOBT) every 3 years

3. Which one of the following CRC prevention therapies is best to recommend for K.G.?

   A. Aspirin 81 mg by mouth daily
   B. Celecoxib 200 mg by mouth daily
   C. Ibuprofen 200 mg by mouth daily
   D. Sulindac 150 mg by mouth daily

Questions 4 and 5 pertain to the following case.

M.T. is a 54-year-old African American woman with obesity. Her family history is positive for her father given a diagnosis of CRC at age 58. M.T.'s medical history is significant for diabetes and hypertension. She consumes 1 or 2 alcoholic drinks per day. M.T. had her first menstrual period at age 10 years, and she was 22 years when she had her daughter.

4. Which one of the following breast cancer prevention strategies is best to recommend for M.T.?

   A. Anastrozole 1 mg orally daily x 5 years
   B. Bilateral mastectomy
   C. Tamoxifen 20 mg orally daily x 5 years
   D. No preventive therapy recommended

5. Which one of the following would be the optimal age for M.T. to begin CRC screening?

   A. 30 years
   B. 40 years
   C. 50 years
   D. 55 years

Questions 6–8 pertain to the following case.

L.D. is a 32-year-old white woman whose mother and sister both died of breast cancer before age 50. Genetic testing shows that L.D. is *BRCA2* positive. She has two daughters (age 6 and 4 years). L.D.'s social history is significant only for a 20 pack-year history of smoking.

6. Which one of the following breast cancer prevention strategies is most likely to reduce L.D.'s risk of developing breast cancer by 90%?

   A. Anastrozole 1 mg orally daily x 5 years
   B. Bilateral mastectomy
   C. Bilateral salpingo-oophorectomy
   D. Tamoxifen 20 mg orally daily x 5 years

7. Which additional cancer-screening test is best to recommend for L.D.?

   A. Cervical cancer
   B. CRC
   C. Endometrial cancer
   D. Lung cancer

8. L.D. wishes to have more children but is concerned about her risk of developing ovarian cancer. Which one of the following options would best decrease L.D.'s risk of ovarian cancer while preserving her ability to conceive?

   A. Anastrozole 1 mg orally daily x 10 years
   B. Bilateral salpingo-oophorectomy
   C. Ethinyl estradiol 20 mcg/drospirenone 3 mg orally daily x 21 days every 28 days
   D. Tamoxifen 20 mg orally daily x 10 years

9. A 19-year-old man with HIV infection comes to the clinic. Which one of the following educational points about the 9-valent human papillomavirus (HPV) vaccine is best to give this patient?

   A. It protects against anal cancer and genital warts.
   B. It protects against anal and oropharyngeal cancer.
   C. It protects against anal and penile cancer and genital warts.
   D. It protects against anal, penile, and oropharyngeal cancer.

10. According to the latest immunization guidelines, an 11-year-old African American boy should receive the 3-injection series of the HPV vaccine. Which one of the following vaccines is best to recommend for this patient?

    A. Bivalent
    B. Quadrivalent or 9-valent
    C. Any of the three: bivalent, quadrivalent, or 9-valent
    D. Bivalent or quadrivalent

Questions 11–13 pertain to the following case.

L.P. is a 55-year-old Asian American woman with a 38 pack-year smoking history. Her pertinent medical history includes hypertension and a hysterectomy with removal of cervix. L.P.'s home drugs include amlodipine. She has a 5-year cumulative breast cancer risk of 1.5%.

11. After discussing risk-benefit with her health care provider, which one of the following is best to recommend for L.P.?

    A. Breast cancer screening with breast MRI yearly
    B. Lung cancer screening with low-dose CT scan yearly
    C. Skin cancer screening with annual health care provider skin examinations
    D. Cervical cancer screening with Pap smear and HPV test every 3 years

12. L.P. is eligible for CRC screening beginning at age 50. Which one of the following CRC screening tests is best to recommend for L.P.?

    A. Colonoscopy every 10 years
    B. CT colonography every 5 years
    C. FIT every 5 years
    D. Flexible sigmoidoscopy every 10 years with or without sensitive gFOBT

13. L.P. wishes to decrease her risk of breast cancer and CRC. She asks you about whether medications can prevent breast cancer or CRC. Which one of the following best answers L.P.'s question?

    A. Aspirin 81 mg by mouth daily for CRC prevention and no preventive therapy for breast cancer.
    B. Aspirin 81 mg by mouth daily for CRC prevention and tamoxifen 20 mg by mouth daily for breast cancer prevention.
    C. No preventive therapy for CRC and tamoxifen 20 mg by mouth daily for breast cancer prevention.
    D. No preventive therapy for either CRC or breast cancer.

14. A 50-year-old healthy Asian man asks your recommendation for cancer screening. Because his brother had complications with prostate cancer screening (false-positive results, incontinence after biopsy), the patient has concerns. Which one of the following guideline recommendations seems most reasonable in this patient?

    A. Begin annual digital rectal examination (DRE) screening now, according to the ACS guidelines.
    B. Begin annual prostate-specific antigen (PSA) screening now, according to the AUA guidelines.
    C. Begin biannual PSA plus annual DRE screening, according to the NCCN.
    D. No prostate cancer screening is recommended, according to the USPSTF guidelines.

15. A 55-year-old white woman has no risk factors for breast cancer other than age and sex. She is a self-employed housekeeper and finds yearly mammography difficult to schedule and a hardship to pay for. So far, she has had no positive mammography findings. According to national guidelines, which one of the following is the most appropriate frequency of mammography to recommend for this patient?

    A. Yearly
    B. Every 2 years
    C. Every 5 years
    D. Only if symptoms develop

16. A 42-year-old premenopausal white woman has a family history that includes her mother and two maternal aunts dying of breast cancer at 70–80 years of age. Her 54-year-old sister was recently given a diagnosis of breast cancer. The patient's genetic testing did not reveal a *BRCA1* or *BRCA2* mutation; however, her calculated 5-year breast cancer risk is 2%. She has no other pertinent medical history, and her only medication is a levonorgestrel-releasing intrauterine device. Which one of the following breast cancer prevention strategies is best to recommend for this patient?

    A. Anastrozole 1 mg orally daily x 5 years
    B. Bilateral mastectomy
    C. Raloxifene 60 mg orally daily x 5 years
    D. Tamoxifen 20 mg orally daily x 5 years

17. A 63-year-old white man has a 45 pack-year history of smoking but quit smoking 13 years ago. His medical history is significant for benign prostatic hyperplasia, hypercholesterolemia, and hypertension. He has been receiving low-dose CT lung cancer screening for the past 5 years, all with negative results. Which one of the following is the best time for this patient to stop lung cancer screening?

    A. Now, after 5 years of negative results because exact benefit beyond this is unknown
    B. Age 80 because exact benefit after this age is unknown
    C. Age 83 after 10 years of negative results because exact benefit beyond this is unknown
    D. Age 70 because that is the upper age limit of patients enrolled in studies

18. A 59-year-old African American woman with obesity is evaluated for hypertension in a follow-up at your clinic. Her medical history is significant for cataracts, osteoporosis, diabetes, and hypertension. She began menses at age 11 years and had her first child at 19 years. Her family history is positive for a maternal grandmother with breast cancer. Because a friend received a diagnosis of breast cancer at age 55, the patient asks how to best decrease her own risk of breast cancer. Which one of the following is best to recommend for this patient?

    A. Exemestane 25 mg orally daily
    B. Tamoxifen 20 mg orally daily
    C. Raloxifene 60 mg orally daily
    D. Weight reduction through exercise and dietary changes

Questions 19 and 20 pertain to the following case.

L.M. is a 39-year-old African American man with a family history that includes his father dying of prostate cancer at age 70. L.M. is healthy now but is interested in prostate cancer prevention and screening.

19. Which one of the following is best to recommend for L.M. to decrease his risk of prostate cancer mortality?

    A. Lycopene 15 mg orally daily
    B. Dutasteride 0.5 mg orally daily
    C. Finasteride 5 mg orally daily
    D. No chemoprevention therapy

20. Which one of the following is the best time and prostate cancer-screening method to recommend for L.M.?

    A. DRE beginning at age 45
    B. DRE beginning at age 50
    C. PSA beginning at age 45
    D. PSA beginning at age 50