Cancer Screening and Prevention

By Kellie L. Jones, Pharm.D., BCOP

Reviewed by William D.Figg, Pharm.D., MBA, FCCP, BCPS; and Marianne McCollum, Ph.D., BSPharm, BCPS

Learning Objectives

1. Given an individual's history, determine when cancer screening should be conducted.
2. Discuss the strengths and limitations of current data for the use of chemoprevention in specific tumor types.
3. Identify the role of antioxidant and vitamin supplementation therapy to prevent lung, prostate, and colon cancer.
4. Given an individual's history, recommend whether pharmacologic therapy should be used in chemoprevention of breast, colon, prostate, or cervical cancer.
5. Plan appropriate cancer screening based on evidence-based guidelines for a patient with normal or high risk of developing cancer.

Introduction

During the past 50 years, epidemiologic studies have identified several environmental factors that can contribute to the development of cancer, including smoking, poor nutrition, physical inactivity, alcohol, excessive sun exposure, chronic infections, and obesity. These exposures can be removed or decreased using lifestyle modifications. Exposure to all carcinogens cannot be eliminated, but educating the general public can raise awareness about ways to lower risk by decreasing or removing sources that can influence the development of cancer. This chapter reviews the current evidence-based recommendations for cancer screening and chemoprevention for men and women.

Cancer Screening

Cancer screening modalities date back to 1928, when George Papanicolaou published results showing normal and malignant cytology on cervical, vaginal, and endometrial samples. This test, better known as a Pap smear, was validated as a diagnostic tool in 1943 and introduced to clinical practice in the late 1940s. Mammography was introduced in the 1950s but was not routinely used in clinical practice until the 1980s. Since the widespread availability of these diagnostic tests, cancer screening has dramatically evolved, and many different guidelines are now available to help guide the early detection of cancer. Table 1-1 lists the current American Cancer Society (ACS) cancer screening guidelines.

Screening Guidelines

Breast Cancer

Organizations such as ACS, the National Comprehensive Cancer Network, and the U.S. Preventive Services Task Force (USPSTF) issue guidelines regarding cancer screening. Annually, ACS publishes updates. The last complete update of recommendations for breast cancer screening was published in 2003, to which, in 2007, another recommendation pertaining to the use of breast magnetic resonance imaging as a screening tool in high-risk women was added. Screening for breast cancer in the average-risk population typically involves

Baseline Review Resource

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. A suggested resource for background information on this topic is:

- Zell JA, Meyskens FL. Cancer prevention, screening, and early detection. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. Abeloff's Clinical Oncology, 4th ed. Philadelphia: Churchill Livingstone Elsevier, 2004:361–95.

Abbreviations in This Chapter

ACS	American Cancer Society
BRCA	Breast cancer (gene)
DRE	Digital rectal examination
FAP	Familial adenomatous polyposis
HPV	Human papillomavirus
PSA	Prostate-specific antigen
USPSTF	U.S. Preventive Services Task Force

three components: breast self-examination, clinical examination, and mammography at a defined age. No one test is considered conclusive; therefore, screening typically involves a combination of these modalities.

Breast self-examination has long been viewed as a way for a woman to become familiar with her body and to identify any physical changes. Although this awareness is important, direct evidence to support breast self-examination is lacking. The current recommendation for self-examination is that women may choose to perform self-examination regularly, occasionally, or not at all, starting in their 20s. Women should be informed about the benefits and limitations of breast self-examination. Women who choose to use this method of screening should be taught the correct technique and encouraged to contact their health care professional promptly if any abnormalities are found. Clinical breast examinations should be completed in women aged 20–39 at least every 3 years, then annually starting at age 40, as part of their periodic health examination.

Mammography has been the gold standard for breast cancer screening for many decades. The ACS guidelines recommend mammograms starting at age 40 and annually thereafter. Questions have been raised regarding the benefit of initiating mammography when a woman turns 40 versus starting at age 50. In 2009, USPSTF sparked controversy because of suggested changes in the appropriate use of mammograms. In a pooled analysis of breast cancer mortality evaluating mammography,

Table 1-1. ACS Cancer Screening Guidelines for Average-Risk Individuals

Cancer	Age (years)	Examination	Interval
Breast	20–39	CBE	Q 3 years
	40–49	CBE	Annually
		Mammography	
	50 and older	CBE	Annually
		Mammography	
Colon	50 and older	FOBT or FIT	Annually
		Stool DNA testing	Uncertain
		Flexible sigmoidoscopy	Q 5 years
		Double contrast enema	Q 5 years
		CT colonography	Q 5 years
		Colonoscopy	Q 10 years
Prostate	50 and older	PSA with or without DRE	Annually
Cervical	About 3 years after first intercourse but no later than 21 years	Pap smear	Annually until age 30 years
	30	Pap smear	Annually, but when three negative tests in a row, can screen every 2–3 years
	31–70	Pap smear	Annually
	Older than 70		May discontinue testing if three negative tests in the previous 10 years
	Any age	After hysterectomy for benign reasons, testing can be discontinued	
	Any age	Hysterectomy for CIN, history of DES exposure, history of cervical cancer	Annually for as long as the patient is in reasonable health

ACS = American Cancer Society; CBE = clinical breast examination; CIN = cervical intraepithelial neoplasia; CT = computed tomography; DRE = digital rectal examination; FIT = fecal immunochemical test; FOBT = fecal occult blood test; PSA = prostate-specific antigen; Q = every.

the relative risk (RR) reduction started to increase in women aged 40–49 who were screened with mammography, but the greatest risk reduction was in women aged 60–69. Because the benefits for women in the younger age group did not outweigh the harms of increased anxiety, radiation exposure, and inconvenience caused by false-positive mammograms, USPSTF recommended against routine screening in women aged 40–49. The task force further recommended that women aged 50–74 needed biennial screening rather than annually. Although the RR is lower in younger women, ACS and all the other organizations that publish breast cancer screening guidelines did not change their recommendation for annual mammography starting at age 40. One positive outcome from these controversial recommendations was a heightened awareness by the general public of the breast cancer screening guidelines.

A newer addition to the ACS breast cancer screening guidelines is the recommendation for use of magnetic resonance imaging for women at high risk of developing breast cancer. Women who are considered high risk and who would benefit from magnetic resonance imaging include those who (1) have a known breast cancer (gene) (*BRCA*) mutation, (2) have not been tested but have a first-degree relative with a *BRCA* mutation, and (3) have a lifetime risk of developing breast cancer of about 20% to 25% or more based on risk estimation models evaluating family history. Other groups deemed high risk by ACS and the National Comprehensive Cancer Network include girls and women who have received radiation treatment to the chest between age 10 and 30 years and individuals who carry or have a first-degree relative with a genetic mutation in *TP53* or *PTEN* genes (i.e., Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes).

Magnetic resonance imagining allows the radiologist to have a contrasted view of the soft tissue structures (e.g., fat, glandular tissue, lesions). Sensitivity is increased compared with mammography, but specificity is less than with mammography. This can lead to false-positive results and additional work-ups (e.g., biopsy). Despite false positives, magnetic resonance imaging leads to the detection of more cancers at an earlier stage in these high-risk populations and should only be used in these patients.

Colon Cancer

Recommendations for colorectal cancer screening are provided by ACS, USPSTF, the U.S. Multisociety Task Force, and the American College of Gastroenterology. A 2001 update for high-risk individuals was published by ACS, and complete updates for average-risk patients were published in 2008 by ACS and the U.S. Multisociety Task Force. The many different modalities of colorectal cancer screening are grouped into two categories: (1) tests that primarily detect cancer and (2) tests that can detect cancer and advanced lesions (polyps). Tests that primarily detect cancer (detection tests) include the guaiac fecal occult blood test, the fecal immunochemical test, and stool DNA testing. Tests that detect cancer and advanced lesions (prevention tests) include endoscopic and radiologic examinations such as colonoscopy, flexible sigmoidoscopy, double-contrast barium enema, and computed tomography colonography (virtual colonoscopy).

For an average-risk individual, the ACS screening recommendations include the following: (1) annual fecal occult blood test or fecal immunochemical test (preferred of the two tests), (2) stool DNA testing (the best interval for testing is uncertain), (3) flexible sigmoidoscopy every 5 years, (4) colonoscopy every 10 years, (5) double-contrast barium enema every 5 years, and (6) computed tomography colonography every 5 years. If the patient has access to and is able to pay for it, a colonoscopy every 10 years is the preferred screening examination. If not, an annual fecal immunochemical test is preferred for screening.

Compared with the traditional fecal occult blood test, the newer fecal immunochemical test more specific for blood than guaiac-based tests and is not subject to false-negative results. The fecal occult blood test can have false positives when a patient has eaten red meats or cruciferous vegetables or when he or she has taken vitamin C before testing.

More definitive recommendations are provided for individuals at high risk of colorectal cancer. If an adult has one first-degree relative with colorectal cancer diagnosed when the relative is age 60 years or older, the person should undergo routine screening at age 50, as recommended for an average-risk person. If an adult has one first-degree relative with colorectal cancer diagnosed before the relative is age 60 years, or two first-degree relatives with colorectal cancer at any age, the individual should undergo colonoscopy every 5 years starting at age 40 or 10 years younger than the age of diagnosis of the youngest family member affected.

In families with known genetic mutations, all individuals should undergo genetic counseling and testing when appropriate regardless of age. Screening recommendations for these individuals are more intensive than for an average-risk person, and recommendations differ on the basis of the genetic mutation. Familial adenomatous polyposis (FAP) is an autosomal dominant genetic mutation; individuals who receive a diagnosis of this syndrome will develop colon cancer at some point in their lives. Screening recommendations mirror the pathology of this syndrome. Polyps, which can be numbered in the hundreds to thousands, begin to develop in the teen years; therefore, screening begins at age 10–12 with a colonoscopy or flexible sigmoidoscopy until a colectomy is deemed appropriate.

Another genetic mutation associated with an increased risk of colon cancer is hereditary non-polyposis colorectal cancer (HPNCC). Individuals with this genetic mutation are at risk of endometrial, ovarian, and liver or bile duct cancer. Colon cancer may develop at a younger age, and screening should begin between ages 20–25 years or 10 years before the youngest first-degree relative received the diagnosis. The screening should include a colonoscopy every 1–2 years until age 40 and then annually.

Annual colonoscopies impose a considerable burden on the U.S. health care system, and surveillance after polypectomy is an important contributor to this problem (i.e., dollars associated with repeat colonoscopies and the capacity to do the screening in patients who have undergone a polypectomy). The National Polyp Study evaluated the use of colonoscopy after polypectomy and made recommendations on the appropriate use of this screening test. In those with one or two small polyps (less than 1 cm) and low-grade dysplasia, follow-up colonoscopy should be performed in 5–10 years. In those with 3–10 adenomas, any adenoma of 1 cm or larger, any adenoma with villous feature, or high-grade dysplasia, colonoscopy should be repeated in 3 years, provided that the adenomas have been completely removed. If a patient has more than 10 adenomas on one examination, colonoscopy sooner than every 3 years is recommended on the basis of clinical judgment. These updated guidelines have allowed clinicians to more selectively use colonoscopies in patients who have had a polypectomy, leading to a reduction in the health care burden by decreasing the amount and cost of unnecessary testing.

Prostate Cancer

In 2010, ACS published a complete update of the prostate screening guidelines. The ACS and USPSTF guidelines recommend that men with at least a 10-year life expectancy receive information about both the risks and benefits of prostate cancer screening and use the information to decide whether to undergo screening. For high-risk groups, the new guidelines simply stress the importance of having discussions about screening at specific ages. For men who decide to undergo screening, the recommended test includes an annual prostate-specific antigen (PSA) blood test with or without a digital rectal examination (DRE) starting at age 50. Men should undergo screening yearly if the PSA concentration is greater than 2.5 ng/mL. In patients with a PSA concentration less than 2.5 ng/mL, screening can be extended to every 2 years.

Two large trials recently reported differences in the benefits of prostate cancer screening. In the United States, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (n=76,693) showed no mortality benefit with prostate cancer screening because most cancers identified were early stage disease (stages I and II). The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (n=162,243) revealed a 20% reduction in prostate cancer mortality in men who were screened compared with controls who were not screened. Differences in these trials may account for the differing results. In the U.S. trial, prostate biopsy was recommended for men with a PSA greater than 4 ng/mL or when a DRE revealed a suspicious mass. In the European trial, a PSA concentration of 3 ng/mL was considered the trigger for biopsy without the need of a DRE. In the PLCO trial, 44% of the men had been screened before enrollment compared with only minimal prescreening in the ERSPC trial, perhaps explaining why additional screening did not provide a benefit. In addition, 40% of the men with abnormal test results in the U.S. trial versus 86% in the European trial underwent a biopsy. Contamination, defined as men in the control arm who underwent a PSA test outside the study, was considered high in the U.S. trial (52%) versus the European trial (6%). In summary, these two trials did not clearly identify the potential value of prostate cancer screening or answer the questions initially asked by the studies. Men should have an in-depth conversation with their health care professional to weigh the risks versus benefits of prostate cancer screening. Risks include overdiagnosis (the increase in the number of cancers diagnosed that may have never been found if not screened) and overtreatment (treatment that was unnecessary such as surgery or chemotherapy when the cancer may have never been diagnosed without screening). Many decision aids are available to help men make an informed decision regarding screening. Some organizations that provide information include ACS, the Centers for Disease Control and Prevention, and the Foundation for Informed Medical Decision Making.

A discussion should be conducted to ensure the patient has an understanding of drugs, conditions, and activities that may alter a PSA. Drugs such as finasteride and dutasteride can decrease PSA concentrations, whereas prostatitis, benign prostatic hypertension, prostate manipulation, and ejaculation can increase PSA concentrations.

Cervical Cancer

Widespread screening has decreased the incidence of cervical cancer in the United States by more than 50% during the past 30 years. However, cervical cancer is still a worldwide health problem because many women lack available screening. The most recent ACS update to screening guidelines was in 2002, and the American Congress of Obstetricians and Gynecologists (ACOG) published new recommendations in 2009. The two screening guidelines differ in several respects.

According to ACS, women should begin cervical screening about 3 years after first vaginal intercourse but no later than 21 years of age, and continue annual

screening until age 30. Once a woman reaches age 30 years and has had three negative Pap smears, screening should continue every 2–3 years with traditional cytology methods or liquid-based preparations, or every 3 years with a combined human papillomavirus (HPV) DNA test and traditional or liquid-based preparations. The ACS guidelines recommend that screening continue until age 70 if the woman has an intact uterus. If a woman has three negative tests in 10 years before age 70, all screening can be discontinued. In women who have had a hysterectomy for a benign reason, screening can be discontinued. In women who have had a hysterectomy for cervical intraepithelial neoplasia, a history of in utero diethylstilbestrol exposure, or a history of cervical carcinoma, screening should continue for as long as the woman would benefit from early detection or treatment of cervical cancer.

Because of the low risk of developing cervical cancer at a young age, ACOG recommends that screening start at age 21 without respect to the age of onset of sexual intercourse. Screening before this time may lead to unnecessary anxiety and potential harm (e.g., premature births in women previously treated with excisions for precancerous lesions). Stating that young women are highly unlikely to receive a diagnosis of cervical cancer (0.1% of all cervical cancer cases), ACOG recommends screening every 2 years (with either a conventional Pap smear test or a liquid-based preparation) until a woman is 30 years old. After three negative test results, women with no other risk factors (e.g., history of cervical intraepithelial neoplasia, human immunodeficiency virus [HIV] infected, history of diethylstilbestrol exposure, or immunocompromised) can have screening extended to every 3 years. The ACOG guidelines also recommend discontinuing screening between age 65–70 years after three or more negative cytology tests in the previous 10 years because of the decreasing risk of cervical cancer. Both ACS and ACOG recommend continued screening in women who had a hysterectomy for cervical cancer and not to discontinue routine screening on the basis of age. Many clinicians follow the ACOG recommendations because they are the most recent guidelines.

Melanoma

There are currently no standard recommendations for screening for skin cancer, including melanoma. The ACS guidelines state that a cancer-related checkup should include an examination for many cancers, one of them being melanoma, and education about the risk of sun exposure and ways to minimize exposure. Although the incidence of melanoma has been increasing for the past 3 decades, literature to support routine screening for skin cancer is lacking. The USPSTF guidelines cite the limitations of published trials (e.g., poor design, inadequate power) in the lack of direct association between screening and improved outcomes.

The American Academy of Dermatology recommends monthly self-examination of the skin to help identify moles or marks on the skin that may be melanoma. Examination of the body (front and back, and right and left sides with arms raised) should be conducted with a mirror. Individuals should be instructed to bend elbows and look carefully at their forearms, upper arms, and palms. In addition, they should look at the back of the legs and feet, between the toes, and on the soles of the feet. Using a handheld mirror to examine the back of the neck, back, buttocks, and scalp and parting the hair for a closer look are also recommended. The American Academy of Dermatology also recommends that individuals see a dermatologist annually if they have a strong family history of melanoma (i.e., first-degree relative with melanoma) or a genetic syndrome that increases the risk of developing melanoma (e.g., familial atypical multiple mole syndrome or hereditary dysplastic nevus syndrome). Other high-risk factors include a personal history of melanoma; history of severe, blistering sun burns; tendency to burn and freckle and not tan; more than 50 moles; or taking immunosuppressive drugs.

Other Cancers

Screening is conducted to prevent an individual from dying from a particular cancer or experiencing significant morbidity associated with that cancer. Criteria to consider in developing a screening program include the following. (1) The disease should have high incidence/severity. (2) The natural history of the disease should allow the patient to benefit from early detection. (3) The test should be accurate, safe, accessible, and reasonably affordable for the patient and screening provider. All current screening guidelines are for cancers that occur commonly; however, not all cancers have available screening guidelines to follow. The one major cancer for which adequate screening has not been recommended is lung cancer.

Many trials have been conducted to identify the potential utility of lung cancer screening. Mechanisms such as chest radiography, sputum cytology, and low-dose computed tomography have been studied in the United States and worldwide. In the United States, final results from the National Lung Screening Trial are yet to be published, although results are available for other low-dose computed tomography trials.

The Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) trial reported an increased number of lung cancers diagnosed with the use of low-dose computed tomography compared with those diagnosed in control subjects with a baseline, one-time-only chest radiograph (60 patients [4.7%] vs. 34 patients [2.8%], respectively). Of patients with a lung cancer diagnosis, the same

number died in both arms, and the number of advanced lung cancers diagnosed was the same. The incidence of false-positive results in lung cancer screening has also been a concern. In a review of the Lung Screening Study (a feasibility study in the ongoing PLCO trial), the probability of a false-positive result was as high as 33% after two screenings with low-dose computed tomography. Findings such as these can lead to unnecessary anxiety and invasive diagnostic procedures for patients and increased costs for health care systems. More mature data will likely define the impact of lung cancer screening on mortality more fully.

Another large lung cancer screening study, the PLCO trial, was opened in 1993. More than 77,000 individuals were recruited and randomly assigned to either chest radiography or usual care for lung cancer screening. Of cancers diagnosed, 54% were screen-detected cancers (diagnosed within 9 months from a positive screen) and 32% were interval-detected cancers (unscreened patients). A significant number of the cancers diagnosed were early stage. Final results regarding the effect of lung cancer screening on mortality are anticipated at the end of 2015. For these reasons, experts do not currently recommend for or against lung cancer screening.

Other less-common cancers also lack standard screening recommendations. The ACS guidelines encourage individuals to undergo periodic examinations by their physicians for cancer. The examination should include an assessment of thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as appropriate. In addition, the physician should discuss self-examination techniques for breast, testicular, and skin cancers. Health-related counseling can review important prevention issues such as smoking cessation, diet, sun exposure, and physical activity.

Screening Limitations

Lead Time Bias

The concept of lead time bias should be reviewed when discussing cancer screening to help distinguish the true benefit in survival. Lead time is the difference between the time a screening test detects a cancer and the time that a patient would have received a diagnosis of that cancer on the basis of symptoms. A fundamental goal in screening is to detect the cancer at an earlier stage when it can be treated effectively and survival can be improved. Bias is introduced when a survival benefit from the screening test is reported, even though a benefit is not actually present (i.e., the survival time appears longer because screening detected the cancer sooner). If survival is the same as would be expected without screening, lead time bias is created. An example of lead time bias is described above with the use of low-dose computed tomography for lung cancer screening. More lung cancers were diagnosed, but no difference in survival rate was identified, even when the cancer was diagnosed earlier.

Overdiagnosis

The purpose of cancer screening is to help diagnose cancer at an earlier stage and to affect survival rates. Effective screening can lead to an overdiagnosis of cancers that are considered indolent and would likely not cause symptoms or affect a person's survival. The increase in prostate cancers diagnosed with the introduction of PSA testing is an example. In the 1980s, the lifetime risk of a man developing prostate cancer was 1 in 11. When PSA testing was routinely made available in the 1990s, the risk increased to 1 in 6. In general, prostate cancer is a slow-growing disease, and most men die of causes other than their prostate cancer. Overdiagnosis can lead to unwarranted anxiety, testing, surgery, treatment, and medical costs. Research is ongoing to help identify biomarkers that differentiate patients with high-risk and low-risk disease and to develop tools to help individuals make more informed decisions on the utility of cancer screening.

Chemoprevention

The use of cancer prevention in the literature dates back to 1727, when it was suggested that the surgical removal of polyps and masses prevented cancer. The influence of diet was documented as early as 1829, when it was identified that changes in eating habits (deprivation of vitamin A) in rats was associated with cancer development. The term *chemoprevention* (i.e., the use of pharmacologic or natural agents to inhibit DNA damage that initiates carcinogenesis) was coined in 1976 by Michael Sporn. His research started with the study of vitamin A, and in the intervening years, innumerable studies have evaluated its use together with other vitamins for the prevention of cancer. Prevention can be accomplished through the use of pharmaceutical agents or nutrients or by surgical procedures to remove the potential source of a cancer. Depending on the patient and his/her medical history, a decision can be made whether one or multiple modalities will be beneficial, especially if the patient has a known cancer in the family or is considered at high risk of developing a cancer.

Breast Cancer

Tamoxifen, Raloxifene, and Retinoids

Tamoxifen has been the gold standard of hormonal therapy for the treatment of early breast cancer for many years. Because of its efficacy for adjuvant and metastatic cancer treatment, tamoxifen was tested as a preventive therapy. In 1998, the National Surgical Adjuvant Breast and Bowel Project P-1 study was published. In this trial, 13,388 women were randomized to receive either tamoxifen 20 mg orally daily for 5 years or placebo. Entry to the trial required that a woman be identified as at high risk of developing breast cancer, which included the following: age 60 years or older; age 35–59 years

with a 5-year predicted risk of developing breast cancer of 1.66% or more calculated using the Gail risk model (a computer-based program that uses personal and family medical history); or the presence of lobular carcinoma in situ (a known risk factor for the development of breast cancer). After 5 years of therapy, tamoxifen reduced the overall risk of invasive breast cancer by 49% compared with placebo. The reduced risk was identified across all age groups and in women with a history of lobular carcinoma in situ. Tamoxifen also reduced the risk of noninvasive cancers by 50%. Adverse effects, which occurred more often in women older than 50 years, included stroke, pulmonary embolism, deep venous thrombosis, and endometrial cancer. Although the risk of thrombosis and endometrial cancer is low with tamoxifen therapy, these potentially serious toxicities should be discussed with the patient. Patients should also be educated on what to look for and what to do if they experience abnormal uterine bleeding or swelling, redness, or pain in the lower extremities. In 1998, tamoxifen received the labeled indication for breast cancer prevention. Both USPSTF and the American Society of Clinical Oncology have published recommendations for the use of tamoxifen for chemoprevention in patients who are at high risk as defined in the National Surgical Adjuvant Breast and Bowel Project P-1 study.

Raloxifene, another selective estrogen receptor modulator, has also been studied for breast cancer prevention. This agent is used for the treatment of osteoporosis. In the osteoporosis trials, patients who received raloxifene were found to have a decreased risk of developing breast cancer. This led to the P-2 trial, the Study of Tamoxifen and Raloxifene (STAR). In this trial, women were randomized to receive tamoxifen 20 mg or raloxifene 60 mg orally daily for 5 years. Inclusion criteria included a 5-year breast cancer risk of 1.66% predicted by the Gail model, age at least 35 years and postmenopausal, and no tamoxifen or raloxifene therapy for at least 3 months before enrollment. No difference in the number of invasive breast cancers was identified between treatment arms. Of interest, more noninvasive breast cancers were identified in the raloxifene arm; however, the difference between treatments was not statistically significant. Thromboembolic events were reported less often with raloxifene than with tamoxifen. Based on results from this trial, raloxifene received a labeled indication for breast cancer prevention in 2007. Phase 3 trials are under way to evaluate the use of aromatase inhibitors for breast cancer prevention; however, no data have been published.

Fenretinide, a synthetic derivative of all-*trans*-retinoic acid, has shown inhibition of carcinogenesis in preclinical and animal models. In 2006, results were published from a phase III study after 15 years of fenretinide therapy for prevention of a second breast cancer. The number of second breast cancers was reduced with fenretinide compared with no treatment. However, questions regarding the data were subsequently raised. Results were not reported for 40% of patients, with no explanation for the reason. Research with this agent used alone or in combination with other agents for the prevention of breast cancer should continue. Currently, fenretinide is not recommended as chemoprevention for breast cancer.

Colon Cancer

Celecoxib, Aspirin, and Nonsteroidal Anti-inflammatory Agents

Studies have evaluated the use of aspirin, cyclooxygenase inhibitors, and nonsteroidal anti-inflammatory agents to decrease the number of colon polyps, which can be a precursor or clinical marker for the development of colorectal carcinoma. These agents have been identified as potential therapies because animal studies have shown inhibition of tumor growth caused by cellular proliferation and inhibition of cyclooxygenase. However, no studies to date have used colorectal cancer mortality as an end point. In addition, no clinical trials have shown any effect in the primary prevention of colorectal cancer in the patient at average risk. Evidence does support the use of aspirin to delay the development of adenomas but only after 10 years of follow-up. Based on the lack of data to show these drugs decrease colon cancer mortality and the potential adverse effects a patient may experience, USPSTF does not recommend the routine use of aspirin, cyclooxygenase inhibitors, or nonsteroidal anti-inflammatory drugs for colorectal cancer prevention in the average-risk patient.

In patients with FAP, the benefits of preventive therapy far outweigh the toxicities. Preventive studies have shown the benefit of celecoxib in patients with FAP by decreasing the polyp burden. Celecoxib is indicated for use in patients with FAP on the basis of a study in which patients were randomized to receive 100 mg, 400 mg, or placebo two times/day. Results showed a statistically significant reduction in the primary end point of the number of polyps in patients randomized to the 400-mg arm and a significant decrease in the polyp burden and number of rectal polyps (which could evolve to invasive cancer over time). Adverse effects were similar across all three treatment arms, with diarrhea and abdominal pain reported most often. Use of any other agents or chemopreventive therapies in other populations is not recommended because of the lack of data and the risk of adverse effects.

Prostate Cancer

Finasteride and Dutasteride

Prostate cancer is an indolent cancer, but mortality may be reduced with early diagnosis. Prostate cancer is hormonally mediated, specifically by androgens. Drugs that alter androgen concentrations or the potency of

testosterone could serve as options to prevent prostate cancer. Finasteride and dutasteride, 5-α-reductase inhibitors, are two such drugs. Finasteride is selective for the 5-α-reductase type 2 isoenzyme and dutasteride is selective for both type 1 and type 2 isoenzymes of 5-α-reductase. The Prostate Cancer Prevention Trial (PCPT) was the first large trial to evaluate the use of finasteride for chemoprevention. A 25% reduction in prostate cancer was reported in the finasteride arm compared with placebo. However, a larger number of patients in the finasteride arm who developed prostate cancer had a higher grade, more aggressive cancer, denoted with a higher Gleason score. The Gleason score is a histologic score ranging from 2 to 10 that indicates how likely it is that a tumor will spread. After the results were published, many researchers evaluated the trial results and identified several biases with the data. With the secondary analysis, the risk reduction of prostate cancer was 21.1% in the placebo arm and 14.7% in the finasteride arm (over a 30% risk reduction for all prostate cancers) with a nonsignificant increase in higher grade tumors. In March 2009, both the American Society of Clinical Oncology and the American Urological Association recommended that physicians discuss the use of finasteride to prevent prostate cancer with men who are at high risk.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial is the most recent trial published evaluating chemoprevention for prostate cancer. The RR reduction with dutasteride was similar to the results seen with finasteride. There was no significant increase in diagnoses of higher-grade prostate cancers in the dutasteride arm. Both trials showed that 5-α-reductase inhibitors decrease the risk of prostate cancer in these patients.

Cervical Cancer

HPV Vaccines

The recent approval of two HPV vaccines will affect the decrease in the incidence of cervical cancer; however, it will take decades to see these results. These vaccines could greatly affect incidence rates if they were routinely made available to women around the world. Human papillomavirus is the driving factor in the development of cervical cancer. These vaccines, if administered appropriately, can prevent HPV infection. In someone who has already been exposed to HPV, the vaccine confers a lower level of protection.

The two most common types of HPV associated with cervical cancer are HPV-16 and HPV-18; both are included in the commercially available vaccines. The quadrivalent vaccine also covers HPV-6 and HPV-11, which are common strains known to cause genital warts. Both vaccines are given as a three-shot series of intramuscular injections. The bivalent vaccine is given at 0, 1, and 6 months, whereas the quadrivalent vaccine is administered at 0, 2, and 6 months. Both are indicated by the Centers for Disease Control and Prevention to be administered to girls starting at age 11 or 12 or in girls and women aged 13–26 if they have not been previously vaccinated.

Men can also be exposed to HPV, and rates of penile, oral, and anal HPV-related cancers in the developed world are similar to those of cervical cancer. When tested in boys and men aged 16–23, the quadrivalent vaccine showed an 86% reduction in persistent HPV infection in the external genital area among all HPV types. On the basis of these data, an indication for boys and men aged 9–26 was added to the quadrivalent vaccine label for the prevention of genital warts.

Many questions remain about the use of these products. One question is with respect to a booster dose. How long are the titers considered high enough to maintain immunity against HPV? There is concern that if an adolescent girl receives the dose at age 11, she will not incur enough immunity to last through the most likely time to acquire and develop HPV. What happens if the patient does not complete the full three-dose course as recommended? What will be the indications for boys and men on the basis of data from future studies? These questions must be answered to help clinicians recommend these vaccines appropriately. In addition, global access to these products is crucial to make an impact on diseases that are of more concern worldwide than in the developed world, where Pap smear tests are readily accessible to women.

Ovarian Cancer

Oral Contraceptives

No screening test is available for early identification of ovarian cancer; therefore, many patients present with an advanced stage of the disease. However, women who are considered at high risk of developing ovarian cancer have options for risk reduction. Oophorectomy is the most obvious prevention method. For women who do not wish to have children or who are postmenopausal, surgery provides a way to decrease their risk of developing ovarian cancer.

Oral contraceptives have long been associated with decreased risk of ovarian cancer. The length of therapy and the amount of estrogen in the oral contraceptive product is strongly correlated with decreased ovarian cancer risk. In the 1960s and 1970s, the amount of estrogen in these products was upward of 100 mcg; today's products contain as little as 30 mcg of estrogen component. In a large meta-analysis of 45 epidemiology studies including more than 23,000 women with ovarian cancer and more than 87,000 women without ovarian cancer, the risk reduction of ovarian cancer was 58% in the women who took oral contraceptives for 15 or more years. Women who took oral contraceptives for 1–4 years showed a 22% decreased risk of developing

ovarian cancer. No other factors (e.g., age at first and last use of the oral contraceptive, use of the oral contraceptive before or after childbirth) contributed to the decreased incidence of ovarian cancer. The protection continued for up to 3 decades after the use of oral contraceptives. Oral contraceptives offer an option for chemoprevention in women who are at high risk of developing ovarian cancer. A full list of agents indicated for use as chemoprevention is provided in Table 1-2.

Antioxidant and Vitamin Supplementation

In the 1960s, studies evaluating vitamin A led to the creation of retinoids, which continue to be evaluated for cancer prevention. Two early epidemiology trials that documented worsening results with the use of vitamin supplementation were the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial, conducted in Finland, and the Beta-Carotene and Retinol Efficacy Trial (CARET), conducted in the United States. Both trials evaluated decreases in lung cancer rates. The ATBC trial included more than 29,000 male smokers aged 50–69 with a mean pack-year history of 36 years. The men received 20 mg of beta carotene plus 50 international units of vitamin E for 6.5 years. More lung cancer cases were diagnosed and more deaths overall occurred in individuals who received supplementation. The CARET outcomes were similarly negative. More than 14,000 men and women who were current or former smokers received beta carotene 30 mg daily plus retinyl palmitate 25,000 international units daily. Of those enrolled, 4060 men had been exposed to occupational asbestos. Lung cancer and mortality rates were increased with the use of beta carotene compared with control. Studies are still under way evaluating the use of these agents in chemoprevention.

In a secondary analysis of a melanoma trial, patients receiving selenium had a 65% reduction in prostate cancer; hence, selenium was chosen as an ideal agent to use for prostate cancer prevention. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) evaluated the effect of selenium and vitamin E use on the risk of prostate and other cancers. The SELECT is the largest chemoprevention study, conducted in more than 35,000 patients. Men were randomized to four treatment arms: selenium plus vitamin E, selenium plus placebo, vitamin E plus placebo, or placebo plus placebo.

Table 1-2. Drug Therapy for Chemoprevention

Cancer	Agent	Dose	Common Toxicities
Breast	Tamoxifen	20 mg PO daily x 5 years	More common: hot flashes, nausea/vomiting, arthralgias Less common: thrombosis, endometrial cancer
	Raloxifene	60 mg PO daily x 5 years	More common: hot flashes, arthralgias, nausea/vomiting Less vomiting: thrombosis
Colon For patients with FAP	Celecoxib	400 mg PO two times/day	More common: abdominal pain, diarrhea Less common: gastrointestinal bleeding, ulceration, cardiovascular thrombotic events
Prostate Agents may be considered in high-risk patients	Finasteride	5 mg PO daily x 7 years	More common: impotence, erectile dysfunction, loss of libido Less common: increased urinary urgency/frequency, dizziness
	Dutasteride	0.5 mg PO daily x 4 years	More common: erectile dysfunction, decreased libido Less common: gynecomastia, loss of libido
Cervical	HPV vaccine (6, 11, 16, 18)	0.5 mL IM at 0, 2, and 6 months	More common: headache, fever, pain, erythema, and swelling at the injection site
	HPV vaccine (16, 18)	0.5 mL IM at 0, 1, and 6 months	More common: fatigue, myalgias, pain, erythema, and swelling at the injection site
Ovarian cancer Agents may be considered in high-risk patients	Oral contraceptives	PO daily	More common: bloating, thromboembolism, breast tenderness Less common: nausea/vomiting, changes in menstrual flow, spotting

FAP = Familial adenomatous polyposis HPV = human papillomavirus; IM = intramuscularly; PO = orally.

The primary end point was biopsy-confirmed prostate cancer. The trial was initially planned for 12 years; however, the study was terminated after an interim analysis at 7 years found no reduction in the risk of prostate cancer by either of the agents alone or in combination. There was also no difference in the incidence of lung or colorectal cancers or of all cancers combined. None of these studies showed benefit in decreasing cancer risks with vitamin and nutrient supplementation; hence, no approval has been granted for vitamin use as chemoprevention.

Impact of Cancer Screening and Prevention

On the basis of projections of cancer incidence rates, it is anticipated that the number of cancer cases will more than double between 2000 and 2050 (1.36 million vs. 3 million). Because of this anticipated increase in the incidence of cancers, it is critical to identify and use standardized cancer screening tools appropriately to diagnose cancer earlier.

The Surveillance, Epidemiology, and End Results (SEER) program recently analyzed age-standardized death rates for all cancers; a net decline in overall mortality was identified from 1970 to 1990 in both men and women. The decline in cancer death rates was attributed to decreased tobacco use, increased screening, and improved cancer treatments. Since the approved coverage of mammography by Medicare, the breast cancer mortality rate has decreased by about 27% in the United States. The number of cervical cancer deaths has also dramatically decreased in the United States with the use of Pap smears. It is estimated that the incidence of invasive cervical cancer has been decreased up to 90% with the use of cervical cancer screening.

Health care professionals should know the recommended screening guidelines and be able to identify individuals who would benefit from the different screening modalities. Even with the known benefit of screening, adherence to screening recommendations for mammograms, Pap smears, and colonoscopies has recently declined. Many factors could affect this drop in participation rates. One could be the lack of public awareness of the recommended guidelines, although many organizations advertise on television, on the radio, in magazines and newspapers, on the Internet, and through national fundraising events for money and increased awareness about cancer research. Another reason for the lack of adherence could be access to the screening tool. Funding for portable mammography and other programs has been created to help subsidize costs, but it does not help all individuals seeking cancer screening. Data have shown that individuals with insurance coverage are more likely to undergo routine cancer screening. The ACS guidelines report that cervical cancer screening is completed less often in women without insurance than in those who are insured (60% vs. 81% completing Pap smear tests in the past 3 years). Women who lack insurance report getting mammograms less than half as often as women who have insurance (26% vs. 56%). In colorectal and prostate cancer screening, race, ethnicity, and socioeconomic factors are more likely to drive an individual to undergo screening than are insurance coverage or level of education. Pharmacists should encourage patients to undergo routine cancer screening and, if needed, seek help from organizations such as ACS for affordable cancer screening options.

Costs and savings can be a benefit or detriment to cancer screening and prevention. Many cost-effectiveness analyses are ongoing to evaluate the benefits of cancer screening and prevention. In a recent cost-effectiveness analysis of prostate cancer, the cost of a quality-adjusted life year (QALY) gained was $122,747 when finasteride was administered to men older than 50 compared with men who received placebo. The authors concluded that this agent was not cost-effective in all men solely on the basis of age, and the patient and physician should discuss whether to start therapy.

Many cost-effectiveness analyses have been conducted of the HPV vaccines in the United States and abroad. In a review of 11 studies, cost-effectiveness was defined at or below $100,000 per QALY gained. When adding in the population of patients to "catch up" on vaccinations, the dollar amount increased to more than $100,000 per QALY gained. The author stated that current cost-effectiveness analyses may underestimate the QALYs gained because of changes in coverage of these products, and over time, the benefits may be offset by some of the direct and indirect costs of disease management. These are just two examples of cost-effectiveness analyses that have been published; many more are in press or ongoing. Costs and savings should always be considered when determining the effectiveness and utility of cancer screening and prevention.

Conclusion

Cancer screening and prevention have evolved during the past several decades. Prevention can include surgery, pharmaceutical agents, or nutrients and/or antioxidant therapy. Several recommendations are in place for the prevention of certain cancers, including breast, colon, prostate, cervical, and melanoma cancer. Several drugs have been approved for use as chemoprevention in high-risk individuals. All health care professionals should be aware of the current screening guidelines and prevention strategies to better educate the public about the potential impact of cancer screening and prevention on cancer mortality rates.

Annotated Bibliography

1. Lippman SM, Hawk ET. Cancer prevention: from 1727 to milestones of the past 100 years. Cancer Res 2009;69:5269–84.

   This article is a thorough review of the evolution of cancer prevention, starting as early as 1727. The publication begins with a historical perspective on the use of surgical modalities to remove potentially cancerous masses. Surgery is still performed in high-risk patients to prevent cancer. The study of vitamin A dates back to as early as 1925, but the widespread evaluation of vitamin E as a chemopreventive agent took form in the 1960s. The ATBC, CARET, and SELECT trials are reviewed in this publication. The evolution of other agents and prevention strategies such as HPV vaccines, oral contraceptives, tobacco cessation, screening, and obesity are also reviewed. This historical compilation of information gives true insight into the evolution of cancer screening and prevention and how we have progressed to where we are today. A timeline is included, as is a pictorial history of the researchers who have been instrumental in the study of cancer prevention.

2. Smith RA, Cokkinides V, Brooks D, Saslow D, Brawley OW. Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin 2010;60:99–119.

   Annually, ACS publishes reports of cancer screening guidelines in *CA: A Cancer Journal for Clinicians*. Many institutions follow these guidelines because they typically are more stringent than other published cancer screening guidelines. Information regarding breast, colorectal, prostate, cervical, endometrial, and other cancer-related examinations is included in the publication each year. As each of the different cancer screening guidelines is updated, the journal publishes the changes. The recommendations include specific information regarding the population to be screened, the test or procedure that should be used, and the frequency in which that screening test should be conducted. In addition, ACS compares and contrasts recommendations with those of other organizations, such as the controversial recommendations by USPSTF for the use of mammography. Moreover, the ACS and ACOG recommendations for the use of Pap smear testing in cervical cancer prevention are compared. Cancer screening trends among populations at risk are included. For cervical cancer screening, there was a decline of 1.3% in screening in 2008 compared with 2005. Mammogram use continues to be prevalent, with a small increase in screening between 2005 and 2008 (51.2% vs. 53%). Colon cancer screening is also on the rise, with 53.2% completion rates in 2008 compared with 46.8% in 2005. In addition, the use of prostate cancer screening is increasing, with 44.1% in 2008 compared with 40.7% in 2005. To date, there is insufficient evidence to support screening for endometrial and lung cancers.

3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.

   The results of this trial (the P1 study) led to the approved indication of tamoxifen for breast cancer prevention. More than 13,000 women considered at high risk were randomized to tamoxifen 20 mg orally daily or placebo for 5 years. High-risk women included (1) those 60 years or older, (2) those 35–59 years with a predicted breast cancer risk of 1.66% (based on the Gail risk model), and (3) those with a history of lobular carcinoma in situ. The primary end point was the prevention of breast cancer, and secondary end points included the potential toxicities of tamoxifen (e.g., myocardial infarction, bone fractures). Tamoxifen decreased the risk of invasive breast cancers by 49% ($p<0.00001$). The highest risk reduction occurred in the oldest patients (i.e., those older than 60 years [55%], those aged 50–59 years [51%], and those younger than 49 years [44%]). Patients with lobular carcinoma in situ (a known risk factor for the development of breast cancer) also had a 56% decreased risk of breast cancer. Toxicities were identified in different age groups. Endometrial cancer risk rates were increased in patients who received tamoxifen (risk ratio = 2.53; 95% confidence interval [CI], 1.35–4.97). The risk was increased to an even greater degree in patients older than 50 years (risk ratio = 4.01; 95% CI, 1.70–10.90). In addition to endometrial cancers, the rates of stroke, pulmonary embolism, and deep venous thrombosis were more common in women older than 50 (risk ratio = 1.75, 95% CI, 0.98–3.20; risk ratio = 3.19, 95% CI, 1.12–11.15; and risk ratio = 1.71, 95% CI, 0.85–3.58, respectively). The risk of developing cataracts was also higher in the tamoxifen arm compared with placebo (risk ratio = 1.14; 95%, CI, 1.01–1.29).

4. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 Trial. JAMA 2006;295:2727–41.

   Tamoxifen is labeled for breast cancer prevention. Raloxifene, another selective estrogen receptor modulator, was also found to reduce the risk of breast cancer in a subset population of an osteoporosis trial (Multiple Outcomes of Raloxifene Evaluation; the MORE trial). This led to the formal comparison of tamoxifen with raloxifene in the STAR or P2 trial. More than 19,000 women considered at high risk of developing breast cancer (5-year risk at least 1.66% based on the Gail model) were randomized to receive tamoxifen 20 mg orally daily or raloxifene 60 mg orally daily for 5 years. Only postmenopausal women were included in the trial, unlike the P1 trial, which included both pre- and postmenopausal women. Breast cancer risk reduction and the risk of toxicities were evaluated. No difference in breast cancer risk (risk ratio = 1.02, 95% CI, 0.82–1.28)

was identified between the tamoxifen and raloxifene groups. Of interest was the lower number of noninvasive breast cancers in those who received tamoxifen (57 cases) compared with those who received raloxifene (80 cases). This finding was not statistically significant (RR = 1.40; 95% CI, 0.98–2.0). Regarding toxicities, there was no difference in ischemic heart disease or stroke between treatment arms. Thromboembolic events were reported less often with raloxifene (risk ratio = 0.70; 95% CI, 0.54–0.91). This study showed that raloxifene was as effective as tamoxifen in reducing the risk of breast cancer, with similar toxicities. Researchers are unsure of the clinical impact of the increased number of noninvasive breast cancers seen with raloxifene. These trial results did not alter or prevent raloxifene from receiving a labeled indication for the prevention of breast cancer.

5. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946–52.

   Individuals with FAP always develop colon cancer with this inherited germ line mutation. The cyclooxygenase-2 isoform is induced in response to cytokine release and other growth factors. These factors are present in inflammatory diseases and premalignant lesions (polyps in colon cancer), the reason for studying a cyclooxygenase inhibitor in this tumor type. Patients in this study were randomized to receive celecoxib 100 mg orally two times/day, 400 mg orally two times/day, or matching placebo for 6 months. The primary end point was the regression in the number of polyps. At the end of 6 months, the largest decrease in the number of polyps was identified in the 400-mg arm, with a 28% reduction, compared with 11.9% in the 100-mg arm (p=0.003). Adverse effects were similar in all groups. On the basis of the results obtained in this trial, celecoxib received a labeled indication to reduce the number of polyps in patients with FAP at a dose of 400 mg orally two times/day.

6. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.

   This study is better known as the PCPT (Prostate Cancer Prevention Trial). Prostate cancer is a hormonally mediated cancer specifically driven by androgens. Finasteride, a 5-α-reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, is a likely agent to alter testosterone concentrations in patients at risk of developing prostate cancer. Men older than 55 years with a normal DRE and no other comorbid conditions participated in a 3-month run-in period. If, after that time, their PSA concentration was 3 ng/mL or lower, the men were randomized to receive finasteride 5 mg orally daily or placebo for 7 years. With finasteride use, 25% fewer prostate cancers were diagnosed. The most controversial result from the study was the higher prevalence of high-grade tumors (tumors with a Gleason score of 7, 8, 9, or 10) that developed in the finasteride group. Because of these results, finasteride was not recommended for routine chemoprevention of prostate cancer. After many clinicians raised questions regarding the biases and inaccuracies of the impact of finasteride on high-grade tumors, an appropriate reanalysis of the PCPT trial was conducted. One of the known mechanisms of androgen deprivation therapy is its ability to change the appearance and size of the prostate, resulting in a decrease in the urinary symptoms men experience when taking androgen deprivation therapy for benign prostatic hypertrophy. With a smaller prostate, the probability of detecting prostate cancer is increased when a prostate biopsy is performed. The doctor and the patient should discuss the risks and benefits of therapy.

7. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorse F, et al; REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192–202.

   The REDUCE trial compared dutasteride 0.5 mg orally daily for 4 years with placebo in men aged 50–75 years with a PSA concentration of 2.5–10 ng/mL and one negative prostate biopsy within 6 months of enrollment. At the end of 4 years, the RR reduction with dutasteride was 22.8% (p<0.001), comparable with the findings in the PCPT trial, in which finasteride showed a 25% risk reduction in prostate cancer. No significant increases in high-grade prostate cancers were identified in the dutasteride arm compared with placebo (220 tumors vs. 233 tumors, respectively; p=0.81), unlike the original results with finasteride in the PCPT trial. Efforts were made when evaluating the data to avoid the pitfalls experienced during the PCPT trial. The incidence of adverse events was similar between the dutasteride and placebo treatment arms. New recommendations regarding the use of dutasteride in cancer screening have not been published because of these new data. In addition, longer follow-ups will be needed to evaluate the full impact of reducing the number of prostate cancers and the impact on mortality rates.

8. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303–14.

   This large meta-analysis of 45 epidemiology studies included more than 23,000 women with ovarian cancer and more than 87,000 controls. A strong correlation between ovarian cancer and the years of oral contraceptive use and the dose of estrogen was identified. Before 1970, the typical dose of estrogen in oral contraceptives was 100 mcg or more. During the 1970s and 1980s, the estrogen dose ranged upward of 50 mcg, with more recent estrogen strengths generally less than 30 mcg. In this meta-analysis, the RR of ovarian cancer was 0.42 (99% CI, 0.36–0.49) in women who took oral contraceptives for 15 or more years compared with women without ovarian cancer. Use for at least 15 years

afforded the greatest advantage in decreasing the risk; however, even women who took oral contraceptives for 1–4 years showed a decreased risk of developing ovarian cancer (RR = 0.78; 95% CI, 0.73–0.83) compared with the control arm of women without ovarian cancer. The protective effects continued for up to 30 years after use. On the basis of the results obtained in these studies, it appears that oral contraceptives offer an option of chemoprevention in women at high risk of developing ovarian cancer. The meta-analysis suggested that more than 200,000 ovarian cancers and 100,000 deaths have been prevented with oral contraceptive use.

9. Omenn GS. Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future. Eur J Cancer Prev 2007;16:184–91.

   The primary focus of this review article on the use of chemoprevention in lung cancer is the discussion of two large trials, the ATBC trial conducted in Finland and the CARET study conducted in the United States. In both trials, the primary end point was decrease in lung cancer rates. The ATBC trial included more than 29,000 male smokers aged 50–69 with a mean pack-year smoking history of 36. Participants received 20 mg of beta carotene plus 50 international units of vitamin E for 6.5 years. More lung cancer cases (RR = 1.18; 95% CI, 1.03–1.36) were diagnosed, and more all-cause mortality (RR = 1.08; 95% CI, 1.01–1.16) was reported in individuals who received the active treatment. Of note, the CARET trial showed negative results with active treatment as well. More than 14,000 men and women who were current or former smokers received beta carotene 30 mg plus retinyl palmitate 25,000 international units daily. Of those enrolled in the study, 4060 men had been exposed to occupational asbestos. The overall RR for the development of lung cancer in individuals who received active treatment was 1.28 (95% CI, 1.04–1.57), and the RR for mortality was 1.17 (95% CI, 1.03–1.33). Although these data showed an increased risk of mortality with prevention strategies, chemoprevention studies continue in this population because lung cancer has the highest mortality rate of all cancers.

10. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.

    The SELECT trial was a multicenter, randomized, placebo-controlled trial of more than 35,000 men considered at high risk of developing prostate cancer. African American men older than 50 years, men older than 50 years with a PSA concentration of 4 ng/mL or less, and men with a normal DRE were randomized to four different arms: selenium (200 mcg) with vitamin E (400 international units) daily, vitamin E plus placebo, selenium plus placebo, or placebo daily for 12 years. After a secondary analysis at 7 years, no benefit in the reduction of prostate cancer was identified, so the study was terminated. The primary end point of the trial was biopsy-confirmed prostate cancer; prespecified secondary outcomes included lung, colorectal, and overall primary cancers. The hazard ratios (HRs) for prostate cancer in the three active treatment groups compared with placebo were as follows: vitamin E alone (HR = 1.13; 95% CI, 0.99–1.29); selenium plus vitamin E (HR = 1.05; 95% CI, 0.91–1.20); and selenium alone (HR = 1.04; 95% CI, 0.90–1.18). No other significant differences were identified in any of the other prespecified cancer end points (p>0.15). This is another example of vitamin supplementation not showing benefit in cancer prevention.

11. Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PLoS ONE 2010;5:1–10.

    This article summarizes the trends in declining mortality rates associated with cancer. The information provided, obtained through the SEER database, includes cancer-related mortality rates from 1970 through 2006. This evaluation revealed that overall cancer mortality declined by 21% in men and 12% in women. Decreases in cancer mortality were believed to be associated with reduction in tobacco use, use of cancer screening (to allow earlier detection), and improvements in the efficacy of overall cancer treatments. The analysis also included information on race and ethnicity, and the cancer death rates declined in all ethnic groups across all ages. The authors commented on the use of screening for the different cancer types. According to the National Health Interview Survey, the use of mammography in women older than 50 years increased in 2000 (70%) and then slightly decreased in 2005 (67%). Colorectal screening increased from 27% to 46% from 1987 to 2005. In general, this article provides a good overview of the advances that have been made in reducing cancer-related mortality and serves as a tool for educating the public regarding the importance of cancer screening and prevention.

Self-Assessment Questions

1. A 65-year-old white man with newly diagnosed lung cancer comes to the clinic to discuss his chemotherapy treatment. He has questions regarding the use of multivitamins and herbs/minerals to reduce his risk of additional cancers. His drugs include paroxetine 20 mg once daily, docusate 100 mg orally two times/day as needed for constipation, vitamin E 800 international units daily, and selenium 200 mcg daily. **Which one of the following is most appropriate regarding this patient's use of vitamins, minerals, or herbal products to reduce the risk of lung cancer?**

   A. Add a daily multivitamin.
   B. Discontinue vitamin E.
   C. Add vitamin A.
   D. Discontinue selenium.

2. A 47-year-old premenopausal woman is in good health with no comorbid conditions. Her medical history is significant only for lobular carcinoma in situ. Her family history includes a paternal grandmother with breast cancer diagnosed at age 66. **Which one of the following drugs for breast cancer prevention is best for this patient?**

   A. Raloxifene.
   B. Fenretinide.
   C. Tamoxifen.
   D. Beta carotene.

3. A 42-year-old woman is interested in undergoing breast cancer screening. She does not have a family history of breast cancer. **Which one of the following screening options is most appropriate for this patient?**

   A. Mammography.
   B. Mammography starting at age 50.
   C. Magnetic resonance imaging testing.
   D. Clinical and self-examination of the breast.

4. A 23-year-old woman in a stable, monogamous relationship asks whether she should receive the human papillomavirus (HPV) vaccination. She has had one other sexual partner. **Which one of the following is the best reason for recommending the vaccination to this patient?**

   A. Reduce her risk of HPV.
   B. Protect her partner from HPV.
   C. Reduce her risk of cervical cancer.
   D. Protect against genital warts.

5. A 35-year-old woman undergoes routine Pap smear testing for cervical cancer prevention. Results show atypical cells of unknown significance. Her gynecologist recommends a repeat Pap smear in 6 months, together with HPV testing. Six months later, a repeat examination reveals a normal Pap smear and negative HPV test. **Which one of the following cervical cancer screening recommendations is most appropriate for this patient?**

   A. Annual Pap smears with either conventional or liquid-based cytology.
   B. Pap smear plus HPV DNA testing every 3 years.
   C. Annual Pap smears until three negative tests; then every other year.
   D. Annual Pap smears with no further HPV testing.

6. A 43-year-old man is in generally good health with no family history of colon cancer. Which one of the following recommendations for colon cancer screening would be the best for this patient to initiate when he reaches age 50?

   A. Colonoscopy every 10 years.
   B. Sigmoidoscopy every 5 years.
   C. Annual fecal occult blood test.
   D. Annual fecal immunohistochemical test.

7. A 12-year-old girl has a family history of colon cancer. Her father developed colon cancer at age 38, and her uncle recently received a diagnosis at age 44. The patient's older brother just tested positive for familial adenomatous polyposis. **Which one of the following recommendations regarding colon cancer screening and prevention is best for this girl?**

   A. Start an annual flexible sigmoidoscopy.
   B. Initiate aspirin for prevention of polyps.
   C. Conduct a colonoscopy.
   D. Initiate celecoxib after colectomy.

8. A 35-year-old woman comes to her gynecologist's office for an annual gynecologic examination. She has no family history of breast cancer or lung cancer. Her father received a diagnosis of colon cancer at age 57, and her uncle received a diagnosis of colon cancer at age 55. **Which one of the following is the most appropriate age for this woman to start colon cancer screening?**

   A. 50.
   B. 47.
   C. 35.
   D. 45.

Questions 9–11 pertain to the following case.
P.K. is a 56-year-old white man who recently discussed prostate cancer screening with his physician. He is healthy and currently takes a once-daily multivitamin and over-the-counter antihistamines and decongestants when needed.

9. **Which one of the following treatment options is most appropriate to initiate for prevention of prostate cancer in P.K.?**

   A. Selenium.
   B. Vitamin E.
   C. Selenium plus vitamin E.
   D. No additional therapy.

10. **Which one of the following treatments would be most appropriate as chemoprevention if P.K. were considered at high risk of developing prostate cancer?**

    A. Dutasteride.
    B. Finasteride.
    C. Selenium.
    D. Vitamin E.

11. **Which one of the following counseling points is most important for P.K. regarding therapy for prostate cancer prevention?**

    A. Avoid use of St. John's wort with finasteride.
    B. Common toxicities of dutasteride include dizziness and rash.
    C. Recheck prostate-specific antigen concentrations 6 months after starting dutasteride therapy.
    D. Women should avoid handling finasteride.

12. **The presence of which one of the following conditions places a person at highest risk of developing melanoma?**

    A. Familial atypical multiple mole syndrome.
    B. Many sunburns in the past.
    C. Presence of numerous moles.
    D. Lack of appropriate use of sunscreens.

13. A 24-year-old woman is using oral contraceptives for birth control. She eats a well-balanced diet, exercises regularly, and has started her cervical cancer screening with Pap smear testing. **Which one of the following actions could have the most benefit in this patient in decreasing her risk of developing ovarian cancer?**

    A. Use oral contraceptives for 10 years.
    B. Have children.
    C. Use oral contraceptives for at least 1 year.
    D. Undergo bilateral salpingo-oophorectomy.

14. A 55-year-old woman is in good health with no comorbid conditions. She started receiving annual mammograms at age 40. No abnormalities have been identified. **Which one of the following is the most appropriate method and timing of screening for this patient?**

    A. Film mammography yearly.
    B. Film mammography every 2 years.
    C. Magnetic resonance imaging annually.
    D. Digital mammography annually.

Questions 15 and 16 pertain to the following case.
B.W. is a 55-year-old postmenopausal woman in the clinic today to discuss the use of tamoxifen for breast cancer prevention. Her doctor told her that she should take tamoxifen for 5 years because there is a history of breast cancer in her family. As a pharmacist in the outpatient clinic, you discuss the risks and benefits of tamoxifen therapy with the physician.

15. **Which one of the following statements is the best response to the physician regarding the use of tamoxifen in B.W.?**

    A. She has more risk of toxicities with tamoxifen, and aromatase inhibitors should be an option.
    B. She has less risk of developing deep venous thrombosis with tamoxifen.
    C. She has more risk of developing cataracts with tamoxifen.
    D. She has less risk of endometrial cancer with tamoxifen.

16. **If B.W. were given a prescription for raloxifene instead of tamoxifen, which one of the following adverse effects would be most important to discuss with her regarding the use of raloxifene?**

    A. Endometrial cancer.
    B. Nausea/vomiting.
    C. Myalgias.
    D. Deep venous thrombosis.

17. **Which one of the following screening/prevention programs would be the most important to initiate first in a newly opened cancer center?**

    A. Melanoma.
    B. Lung cancer.
    C. Breast cancer.
    D. Prostate cancer.

18. A 47-year-old woman in good health has not been to the doctor in years because she goes only when she is ill. **Which one of the following is the most important cancer screening recommendation for this patient?**

A. Annual physical examinations should begin now.
B. Cancer screening should be initiated at age 50.
C. Cancer screening should begin now.
D. Breast self-examinations should begin now.

19. A 25-year-old woman has a strong family history of breast cancer; her mother was given a diagnosis of breast cancer at age 38, and two aunts were given diagnoses of breast cancer at ages 37 and 42. The patient is seen by a genetic counselor and, when tested for the breast cancer (gene) *BRCA* mutation, is found to have the mutation. **Which one of the following screening plans is most appropriate for this patient?**

A. Annual mammography starting at age 30.
B. Annual mammography and magnetic resonance imaging starting at age 30.
C. Annual mammography starting now.
D. Annual mammography and magnetic resonance imaging starting now.

20. A 58-year-old man in good health underwent a screening colonoscopy at age 51 that revealed one benign polyp. **Which one of the following agents is best to recommend for chemoprevention of colon cancer on the basis of this patient's history?**

A. Aspirin.
B. Nonsteroidal anti-inflammatory agent.
C. Celecoxib.
D. No therapy.