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Jennifer M. Croswell, Otis W. Brawley,

Barnett S. Kramer

Prevention and Early

Detection of Cancer Improved understanding of carcinogenesis has allowed cancer prevention and early detection to expand beyond identification and avoidance of carcinogens. Specific interventions to reduce cancer mortality by preventing cancer in those at risk and effective screening for early detection of cancer are the goals. Carcinogenesis is a process that usually extends over years, a continuum of discrete tissue and cellular changes over time resulting in aberrant physiologic processes. Prevention concerns the identification and manipulation of the biologic, environmental, social, and genetic factors in the causal pathway of cancer. Examination of national epidemiologic patterns can provide indicators of the relative contributions of advances in prevention, screening, and therapy in progress against cancer, but randomized trials provide the best evidence to guide practice, especially in the healthy general population. EDUCATION AND HEALTHFUL HABITS Public education on the avoidance of identified risk factors for cancer and encouraging healthy habits contributes to cancer prevention. The clinician is a powerful messenger in this process. The patient-provider encounter provides an opportunity to teach patients about the hazards of smoking, influence of a healthy lifestyle and other exposures, and use of proven cancer screening methods. ■ ■SMOKING CESSATION Tobacco smoking is a strong, modifiable risk factor for cardiovascular disease, pulmonary disease, and cancer. Smokers have an ~1 in 3 lifetime risk of dying prematurely from a tobacco-related cancer, cardiovascular, or pulmonary disease, and cigarette smoking shortens life expectancy, on average, by a decade. Tobacco use causes more deaths from cardiovascular disease than from cancer. Lung cancer and cancers of the larynx, oropharynx, esophagus, kidney, bladder, colon, pancreas, stomach, and uterine cervix are all tobacco related. The number of cigarettes smoked per day and the level of inhalation of cigarette smoke are correlated with risk of lung cancer mortality. Light- and low-tar cigarettes are not safer because smokers tend to inhale them more frequently and deeply. Those who stop smoking have a 30-50% lower 10-year lung cancer mortality rate compared to those who continue smoking,

despite the fact that some carcinogen-induced gene mutations persist for years after smoking cessation. Smoking cessation and avoidance would save more lives from cancer than any other public health activity. The risk of tobacco smoke is not limited to the smoker. Environmental tobacco smoke, known as secondhand or passive smoke, is carcinogenic and associated with a variety of respiratory illnesses in exposed children. Tobacco use prevention is a pediatric issue. More than 80% of adult American smokers began smoking before the age of 18 years. Traditional cigarette smoking has declined substantially in recent years: for example, for high school seniors between 2012 and 2019, prevalence of past 30-day cigarette smoking dropped from 19% to 7% for boys and 7% to 2% for girls. Electronic cigarettes, on the other hand, are rapidly increasing in use: in 2020, approximately 20% of high school students reported being current electronic cigarette users. Counseling of adolescents and young adults is critical to prevent all forms of tobacco use. A clinician's simple advice can be of benefit. Providers should query patients on tobacco use and offer smokers assistance in quitting or referrals to cessation programs. Current approaches to smoking cessation recognize nicotine in tobacco as addicting (Chap. 465). The smoker who is quitting goes

through identifiable stages, including contemplation of quitting, an action phase in which the smoker quits, and a maintenance phase. Smokers who quit completely are more likely to be successful than those who gradually reduce the number of cigarettes smoked or change to lower-tar or lower-nicotine cigarettes. Organized cessation programs may help individual efforts. Heavy smokers may need an intensive broad-based cessation program that includes counseling, behavioral strategies, and pharmacologic adjuncts, such as nicotine replacement (gum, patches, sprays, lozenges, and inhalers), bupropion, and/or varenicline. Electronic cigarettes have been advocated as a tool to achieve smoking cessation or as a harm reduction strategy in adults, but the net effects of electronic cigarettes on health are poorly studied. Absence of strict manufacturing controls of vaping material has produced serious injury.

The health risks of cigars are similar to those of cigarettes. Smoking one or two cigars daily doubles the risk for oral and esophageal cancers; smoking three or four cigars daily increases the risk of oral cancers more than eightfold and esophageal cancer fourfold. The risks of occasional use are unknown. Smokeless tobacco also represents a substantial health risk. Chewing tobacco is linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. The systemic effects of smokeless tobacco (including snuff) may increase risks for other cancers. Esophageal cancer is linked to carcinogens in tobacco dissolved in saliva and swallowed.

CHAPTER 75 ■ ■ PHYSICAL ACTIVITY Physical activity is associated with a decreased risk of colon and breast cancer. A variety of mechanisms have been proposed. However, such studies are prone to confounding factors such as recall bias, association of exercise with other health-related practices, and effects of preclinical cancers on exercise habits (reverse causality).

Prevention and Early Detection of Cancer ■ ■ DIET MODIFICATION International ecologic studies suggest that diets high in fat are associated with increased risk for cancers of the breast, colon, prostate, and endometrium. Despite correlations, dietary fat has not been proven to cause cancer. Case-control and cohort epidemiologic studies give conflicting results. Diet is a highly complex exposure to many nutrients and chemicals. Low-fat diets are associated with many dietary changes beyond simple subtraction of fat. Other lifestyle factors are also associated with adherence to a low-fat diet. In some observational studies, dietary fiber has been associated with a reduced risk of colonic polyps and invasive cancer of the colon. Two large prospective cohort studies of >100,000 health professionals showed no association

between fruit and vegetable intake and risk of cancer, however. Cancer-protective effects of increasing fiber and lowering dietary fat have not been shown in the context of a prospective clinical trial. The Polyp Prevention Trial randomly assigned 2000 elderly persons, who had polyps removed, to a low-fat, high-fiber diet versus routine diet for 4 years. No differences were noted in polyp formation. The U.S. National Institutes of Health Women's Health Initiative, launched in 1994, was a long-term clinical trial enrolling >100,000 women age 45–69 years. It placed women into 22 intervention groups. Participants received calcium/vitamin D supplementation; hormone replacement therapy; and counseling to increase exercise, eat a lowfat diet with increased consumption of fruits, vegetables, and fiber, and cease smoking. The study showed that although dietary fat intake was lower in the diet intervention group, invasive breast cancers were not reduced over an 8-year follow-up period compared to the control group. Additionally, no reduction was seen in the incidence of colorectal cancer in the dietary intervention arm. In the aggregate, cohort studies and randomized trials suggest that reduction of red meat or processed meat consumption has a small (if any) effect on cancer incidence and mortality, although the overall evidence base is weak. Evidence does not currently establish the anticarcinogenic value of vitamin, mineral, or nutritional supplements in amounts greater than those provided by a balanced diet.

■ ■ENERGY BALANCE Risk of certain cancers appears to increase modestly (relative risks generally in the 1.0–2.0 range) as body mass index (BMI) increases beyond 25 kg/m². A cohort study of >5 million adults included in the U.K. Clinical Practice Research Datalink (a primary care database) found that each 5 kg/m² increase in BMI was linearly associated with cancers of the uterus, gallbladder, kidney, cervix, thyroid, and leukemia. High BMI appears to have an inverse association with prostate and premenopausal breast cancer.

■ ■SUN AVOIDANCE Nonmelanoma skin cancers (basal cell and squamous cell) are induced by cumulative exposure to ultraviolet (UV) radiation. Evidence for a direct association between cumulative UV exposure and melanoma is weaker. Reduction of sun exposure through use of protective clothing and changing patterns of outdoor activities can reduce skin cancer risk. Sunscreens decrease the risk of actinic keratoses, the precursor to squamous cell skin cancer, but melanoma risk may not be reduced. Sunscreens prevent burning, but they may encourage more prolonged exposure to the sun and may not filter out wavelengths of energy that cause melanoma. Appearance-focused behavioral interventions in young women can decrease indoor tanning use and other UV exposures and may be more effective than messages about long-term cancer risks. Those who recognize themselves as being at risk tend to be more compliant with sun-avoidance recommendations. Risk factors for melanoma include a propensity to sunburn, a large number of benign melanocytic nevi, and atypical nevi. However, about 70–80% of melanomas arise de novo, rather than from existing benign nevi.

PART 4 Oncology and Hematology CANCER

CHEMOPREVENTION Chemoprevention involves the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy. Cancer develops through an accumulation of tissue abnormalities associated with genetic and epigenetic changes, and growth regulatory pathways that are potential points of intervention to prevent cancer. The initial changes are termed initiation. The alteration can be inherited or acquired through the action of physical, infectious, or chemical carcinogens. Like most human diseases, cancer arises from an interaction between genetics and environmental exposures (Table 75-1). Influences that cause the initiated cell and its surrounding tissue microenvironment to progress through the carcinogenic process and change phenotypically are termed promoters.

Promoters include hormones such as androgens, linked to prostate cancer, and estrogen, linked to breast and endometrial cancer. The difference between an initiator and promoter is indistinct; some components of cigarette smoke are “complete carcinogens,” acting as both initiators and promoters. Cancer can be prevented or controlled through avoidance of the factors that cause cancer initiation, promotion, or progression. Compounds of interest in chemoprevention may have antimutagenic, hormone modulation, anti-inflammatory, antiproliferative, or proapoptotic activity (or a combination).

CHEMOPREVENTION OF CANCERS OF THE UPPER AERODIGESTIVE TRACT

Smoking causes diffuse epithelial injury in the oral cavity, esophagus, and lung. Patients cured of squamous cell cancers of the lung, esophagus, and oral cavity are at risk (as high as 5% per year) of developing second cancers of the upper aerodigestive tract. Cessation of cigarette smoking does not markedly decrease the cured cancer patient’s risk of second malignancy, even though it does lower the cancer risk in those who have never developed a malignancy. Persistent oral human papillomavirus (HPV) infection, particularly HPV-16, increases the risk for cancers of the oropharynx. This association exists even in the absence of other risk factors such as smoking or alcohol use (although the magnitude of increased risk appears greater than additive when HPV infection and smoking are both present). Oral HPV infection is believed to be largely sexually acquired. The use of

TABLE 75-1 Suspected Carcinogens ASSOCIATED CANCER OR NEOPLASM

Alkylating agents	Acute myeloid leukemia, bladder cancer
Androgens	Prostate cancer
Aromatic amines (dyes)	Bladder cancer
Arsenic	Cancer of the lung, skin
Asbestos	Cancer of the lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung cancer
Diethylstilbestrol (prenatal)	Vaginal cancer (clear cell)
Epstein-Barr virus	Burkitt’s lymphoma, nasal T-cell lymphoma
Estrogens	Cancer of the endometrium, liver, breast
Ethyl alcohol	Cancer of the breast, liver, esophagus, head and neck
Helicobacter pylori	Gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma
Hepatitis B or C virus	Liver cancer
Human immunodeficiency virus	Non-Hodgkin’s lymphoma, Kaposi’s sarcoma, squamous cell carcinomas (especially of the urogenital tract)
Human papillomavirus	Cancers of the cervix, anus, oropharynx
Human T-cell lymphotropic virus type 1 (HTLV-1)	Adult T-cell leukemia/lymphoma
Immunosuppressive agents (azathioprine, cyclosporine, glucocorticoids)	Non-Hodgkin’s lymphoma
Ionizing radiation (therapeutic or diagnostic)	Breast, bladder, thyroid, soft tissue, bone, hematopoietic, and many more
Nitrogen mustard gas	Cancer of the lung, head and neck, nasal sinuses
Nickel dust	Cancer of the lung, nasal sinuses
Diesel exhaust	Lung cancer (miners)
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin (especially squamous cell carcinoma of scrotal skin)
Radon gas	Lung cancer
Schistosomiasis	Bladder cancer (squamous cell)
Sunlight (ultraviolet)	Skin cancer (squamous cell and likely melanoma)
Tobacco (including smokeless)	Cancer of the upper aerodigestive tract, bladder, kidney
Vinyl chloride	Liver cancer (angiosarcoma)

aAgents that are thought to act as cancer initiators and/or promoters. the HPV vaccine is associated with a reduction in prevalence of oropharyngeal infection rates and may eventually reduce oropharyngeal cancer rates. Oral leukoplakia, a premalignant lesion commonly found in smokers, has been used as an intermediate marker of chemopreventive activity in smaller shorter-duration, randomized, placebo-controlled trials. Although therapy with high, relatively toxic doses of isotretinoin (13-cis-retinoic acid) causes regression of oral leukoplakia, more tolerable doses of isotretinoin have not shown benefit in the prevention of head and neck cancer. Several large-scale trials have assessed agents in the chemoprevention of lung cancer in patients at high risk. In the α -tocopherol/ β -carotene (ATBC) Lung Cancer Prevention Trial, participants were male smokers with

an average 30-plus pack-year history, age 50–69 years at entry. After median follow-up of 6 years, lung cancer incidence and mortality were statistically significantly increased in those receiving β -carotene. α -Tocopherol had no effect on lung cancer mortality, but patients receiving it had a higher incidence of hemorrhagic stroke. The β -Carotene and Retinol Efficacy Trial (CARET) involved 17,000 American smokers and workers with asbestos exposure. This trial also

demonstrated harm from β -carotene: a lung cancer rate of 5 per 1000 subjects per year for those taking placebo versus 6 per 1000 subjects per year for those taking β -carotene. The ATBC and CARET results demonstrate the importance of testing chemoprevention hypotheses in randomized trials before widespread implementation because the results contradict a number of observational studies. ■ ■CHEMOPREVENTION OF COLON CANCER No agent with sufficient evidence exists at present for the prevention of colon cancer in the general population. A meta-analysis of four randomized controlled trials primarily designed to examine aspirin's effects on cardiovascular events found no association between low-dose aspirin use and colorectal cancer incidence at up to 10 years of follow-up. The same review reported highly variable results for colorectal cancer mortality and aspirin use and noted that, overall, studies have not been adequately powered to assess aspirin's effects on colorectal cancer deaths. As such, the evidence is insufficient that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce colorectal cancer incidence or mortality. However, there is clear evidence that regular NSAID use is associated with important bleeding harms, such as major gastrointestinal and intra- and extracranial bleeding, particularly with increasing dosage and age. Cyclooxygenase-2 (COX-2) inhibitors have been considered for colorectal cancer and polyp prevention. Trials with COX-2 inhibitors were initiated, but an increased risk of cardiovascular events in those taking the COX-2 inhibitors was noted, so these agents are not suitable for chemoprevention in the general population. The Women's Health Initiative demonstrated that postmenopausal women taking estrogen plus progestin have a 44% lower relative risk of colorectal cancer compared to women taking placebo. Of >16,600 women randomized and followed for a median of 5.6 years, 43 invasive colorectal cancers occurred in the hormone group and 72 in the placebo group. The positive effect on colon cancer is mitigated by the modest increase in cardiovascular and breast cancer risks associated with combined estrogen plus progestin therapy, and guidelines do not recommend hormonal therapy as a standard preventive agent for colorectal cancer incidence or mortality. Most case-control and cohort studies have not confirmed early reports of an association between regular statin use and a reduced risk of colorectal cancer. No randomized controlled trials have addressed this hypothesis. A meta-analysis of statin use showed no protective effect of statins on overall cancer incidence or death. ■ ■CHEMOPREVENTION OF BREAST CANCER Tamoxifen is an antiestrogen with partial estrogen agonistic activity in some tissues, such as endometrium and bone. One of its actions is to upregulate transforming growth factor β , which decreases breast cell proliferation. In a randomized placebo-controlled prevention trial involving >13,000 pre- and postmenopausal women at high risk, tamoxifen decreased the risk of developing breast cancer by 49% (from 43.4 to 22 per 1000 women) after a median follow-up of nearly 6 years. Tamoxifen also reduced bone fractures; a small increase in risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis was noted. The International Breast Cancer Intervention Study (IBIS-I) and the Italian Randomized Tamoxifen Prevention Trial also demonstrated reductions in breast cancer incidence with tamoxifen use. A trial comparing tamoxifen with another selective estrogen receptor modulator, raloxifene, performed in postmenopausal women showed that raloxifene is comparable to tamoxifen in cancer prevention but without the risk of endometrial cancer. Raloxifene was

associated with a smaller reduction in invasive breast cancers and a trend toward more noninvasive breast cancers, but fewer thromboembolic events than tamoxifen; the drugs are similar in risks of other cancers, fractures, ischemic heart disease, and stroke. Both tamoxifen and raloxifene (the latter for postmenopausal women only) have been approved by the U.S. Food and Drug Administration (FDA) for reduction of breast cancer in women at high risk for the disease (1.66% risk at 5 years based on the Gail risk model: <http://www.cancer.gov/bcrisktool/>).

Because the aromatase inhibitors (anastrozole, exemestane, and letrozole) are even more effective than tamoxifen in adjuvant breast cancer treatment, it has been hypothesized that they would be more effective in breast cancer prevention. A randomized, placebocontrolled trial of exemestane reported a 65% relative reduction (from 5.5 to 1.9 per 1000 women) in the incidence of invasive breast cancer in women at elevated risk after a median follow-up of about 3 years. Common adverse effects included arthralgias, hot flashes, fatigue, and insomnia. No trial has directly compared aromatase inhibitors with selective estrogen receptor modulators for breast cancer chemoprevention.

■ ■CHEMOPREVENTION OF PROSTATE CANCER Finasteride and dutasteride are 5- α -reductase inhibitors. They inhibit conversion of testosterone to dihydrotestosterone (DHT), a potent stimulator of prostate cell proliferation. The Prostate Cancer Prevention Trial (PCPT) randomly assigned men age 55 years or older at average risk of prostate cancer to finasteride or placebo. All men in the trial were being regularly screened with prostate-specific antigen (PSA) levels and digital rectal examination. After 7 years of therapy, the overall incidence of prostate cancer was 18.4% in the finasteride arm, compared with 24.4% in the placebo arm, a statistically significant reduction. However, the finasteride group had more patients with tumors of Gleason score 7 and higher compared with the placebo arm (6.4 vs 5.1%). Long-term (10–15 years) follow-up did not reveal any statistically significant differences in overall or prostate cancer-specific mortality between all men in the finasteride and placebo arms or in men diagnosed with prostate cancer, but the power to detect a difference was limited. CHAPTER 75 Prevention and Early Detection of Cancer Dutasteride has also been evaluated as a preventive agent for prostate cancer. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a randomized double-blind trial in which ~8200 men with an elevated PSA (2.5–10 ng/mL for men age 50–60 years and 3–10 ng/mL for men age 60 years or older) and negative prostate biopsy on enrollment received daily 0.5 mg of dutasteride or placebo. The trial found a statistically significant 23% relative risk reduction in the incidence of biopsy-detected prostate cancer in the dutasteride arm at 4 years of treatment (659 cases vs 858 cases, respectively). Overall, across years 1 through 4, no difference was seen between the arms in the number of tumors with a Gleason score of 7 to 10; however, during years 3 and 4, there was a statistically significant difference in tumors with Gleason score of 8 to 10 in the dutasteride arm (12 tumors vs 1 tumor, respectively). The finding of an apparent increased incidence of higher-grade tumors likely represents an increased sensitivity of PSA and digital rectal exam for high-grade tumors in men receiving 5- α -reductase inhibitors due to a decrease in prostatic volume. Although detection bias may have accounted for the finding, a causative role cannot be conclusively dismissed. These agents are therefore not FDA-approved for prostate cancer prevention. Because all men in both the PCPT and REDUCE trials were being screened and because screening approximately doubles the rate of prostate cancer, it is not known if finasteride or dutasteride decreases the risk of prostate cancer in men who are not being screened or simply reduces the risk of non-life-threatening cancers detectable by screening. Several favorable

laboratory and observational studies led to the formal evaluation of selenium and α -tocopherol (vitamin E) as potential prostate cancer preventives. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), after a median follow-up of 7 years, found a trend toward an increased risk of developing prostate cancer for men taking vitamin E alone as compared to placebo (hazard ratio 1.17; 95% confidence interval, 1.004–1.36). ■ ■ VACCINES AND CANCER PREVENTION A number of infectious agents cause cancer. Hepatitis B and C viruses are linked to liver cancer; some HPV strains are linked to cervical, anal, and oropharyngeal cancer; and *Helicobacter pylori* is associated with

gastric adenocarcinoma and gastric lymphoma. Vaccines to protect against these agents may therefore reduce the risk of their associated cancers.

The hepatitis B vaccine is effective in preventing hepatitis and hepatomas due to chronic hepatitis B infection. A nonavalent HPV vaccine (covering strains 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available for use in the United States. HPV types 6 and 11 cause genital papillomas. The remaining HPV types cause cervical and anal cancer; reduction in HPV types 16 and 18 alone could theoretically prevent >70% of cervical cancers worldwide. For individuals not previously infected with these HPV strains, the vaccine demonstrates high efficacy in preventing persistent strain-specific HPV infections. Studies also confirm the vaccine's ability to prevent preneoplastic lesions (cervical or anal intraepithelial neoplasia [CIN/AIN] I, II, and III). The vaccine does not appear to impact preexisting infections. A two-dose schedule is currently recommended in the United States for females and males age 9–14 years; teens and young adults who start the series between 15 and 26 years are recommended to receive three doses of the vaccine. However, observational studies suggest similar efficacy with a single dose in young girls, and a large randomized trial is currently comparing one to two doses.

SURGICAL PREVENTION OF CANCER Some organs in some individuals are at such high risk of developing cancer that surgical removal of the organ at risk may be considered. Women with severe cervical dysplasia are treated with laser or loop electrosurgical excision or conization. Colectomy may be used to prevent colon cancer in patients with familial polyposis or ulcerative colitis.

PART 4 Oncology and Hematology Prophylactic bilateral mastectomy may be chosen for breast cancer prevention among women with high-risk genetic predisposition to breast cancer. In a prospective series of 139 women with BRCA1 and BRCA2 mutations, at 3 years, no cases of breast cancer had been diagnosed in those opting for surgery ($n = 76$), but eight of 63 patients in the surveillance group had developed breast cancer. A larger retrospective cohort study reported three patients developed breast cancer after prophylactic mastectomy compared with an expected incidence of 30–53 cases. Postmastectomy breast cancer-related deaths were 81–94% lower in high-risk women compared with sister controls and 100% lower in moderate-risk women when compared with expected rates. Prophylactic salpingo-oophorectomy may also be employed for the prevention of ovarian and breast cancers among high-risk women. A prospective cohort study evaluating the outcomes of BRCA mutation carriers demonstrated a statistically significant association between prophylactic salpingo-oophorectomy and a reduced incidence of ovarian or primary peritoneal cancer (36% relative risk reduction, or a 4.5% absolute difference). Studies of prophylactic oophorectomy for prevention of breast cancer in women with genetic mutations have shown relative risks of approximately 0.50; the risk reduction may be greatest for women having the procedure at younger (i.e., <45–50) ages. The observation that most high-grade serous “ovarian cancers” actually arise in the fallopian tube fimbria raises the possibility that this lethal subtype may be prevented by ovary-sparing salpingectomy. Formal testing of this

hypothesis is important because an emulated target trial (i.e., study design principles of a randomized controlled trial applied to observational data to estimate causal effects) demonstrated associations between bilateral salpingo-oophorectomy during benign hysterectomy and an increased risk for cardiovascular disease when done in premenopausal women and a trend toward increased 10-year mortality in all ages (with statistical significance in perimenopausal women). All of the evidence concerning the use of prophylactic mastectomy and salpingo-oophorectomy for prevention of breast and ovarian cancer in high-risk women has been observational; such studies are prone to a variety of biases, including case selection bias, family relationships between patients and controls, and inadequate information about hormone use. Thus, they may give an overestimate of the magnitude of benefit.

■ ■ CANCER SCREENING

Screening is a means of early detection in asymptomatic individuals, with the goal of decreasing morbidity and mortality. While screening can potentially reduce disease-specific deaths and has been shown to do so in cervical,

colon, lung, and breast cancer, it is also subject to several biases that can suggest a benefit when there is none. Biases can even mask net harm. Early detection does not in itself confer benefit. Cause-specific mortality, rather than survival after diagnosis, is the preferred endpoint (see below). Because screening is done on

asymptomatic, healthy persons, it should offer substantial likelihood of benefit that outweighs harm. Screening tests and their appropriate use should be carefully evaluated before their use is widely encouraged in screening programs. The Accuracy of Screening A screening test's accuracy or ability to discriminate disease is

described by four indices: sensitivity, specificity, positive predictive value, and negative predictive value (Table 75-2).

Sensitivity, also called the true-positive rate, is the proportion of persons with the disease who test positive in the screen (i.e., the ability of the test to detect disease when it is present).

Specificity, or 1 minus the

false-positive rate, is the proportion of persons who do not have the disease who test negative in the screening test (i.e., the ability of a test to correctly indicate that the disease is not present). The positive predictive value is the proportion of persons who test positive and who actually have the disease. Similarly, negative

predictive value is the proportion testing negative who do not have the disease. The sensitivity and specificity of a test are relatively independent of the underlying prevalence (or risk) of the disease in the population screened, but the predictive values depend strongly on the prevalence of the disease. Screening is most beneficial, efficient,

and economical when the target disease is common in the population being screened. Specificity is at least as important to the ultimate feasibility and success of a screening test as sensitivity. Potential Biases of Screening Tests Common biases of screening are lead time, length-biased sampling (and related overdiagnosis), and

selection. These biases can make a screening test seem beneficial when it is not (or even causes net harm).

Whether beneficial or not, screening can create the false impression of an epidemic by increasing the number of cancers diagnosed. It can also produce a shift in the proportion of patients diagnosed at an early stage

(even without a reduction in absolute incidence of late-stage disease) and inflate survival statistics without reducing mortality (i.e., the number of deaths from a given cancer relative to the number of those at risk for the cancer in TABLE 75-2

Assessment of the Value of a Diagnostic Test

CONDITION PRESENT

CONDITION ABSENT Positive

test a b Negative test c d a
= true positive b = false
positive c = false negative
d = true negative

Sensitivity The proportion of
persons with the condition
who test positive: $a/(a + c)$

Specificity The proportion of
persons without the
condition who test negative:
 $d/(b + d)$ Positive predictive
value (PPV) The proportion
of persons with a positive

test who have the condition:
 $a/(a + b)$ Negative predictive
value The proportion of
persons with a negative test
who do not have the
condition: $d/(c + d)$

Prevalence, sensitivity, and
specificity determine PPV
$$\text{PPV} = \frac{\text{prevalence} \times \text{sensitivity}}{(\text{prevalence} \times \text{sensitivity}) + (1 - \text{prevalence}) \times (1 - \text{specificity})}$$

× ×

- — — aFor diseases of low prevalence, such as cancer, poor specificity has a dramatic adverse effect on PPV such that only a small fraction of positive tests are true positives.

the total population). In such a case, the apparent duration of survival (measured from date of diagnosis) increases without lives being saved or life expectancy changed. Lead-time bias occurs

whether or not a test influences the natural history of the disease; the patient is merely diagnosed at an earlier date. Survival appears increased even if life is not prolonged. The screening test only prolongs the time the subject is aware of the disease and spends as a cancer patient. Length-biased sampling occurs because screening tests generally can more easily detect slow-growing, less aggressive cancers than fast-growing cancers. Cancers diagnosed due to the onset of symptoms between scheduled screenings are on average more aggressive, and treatment outcomes are not as favorable. An extreme form of length bias sampling is termed overdiagnosis, the detection of "pseudo disease." The reservoir of some slow-growing tumors is large. Many of these tumors fulfill the histologic criteria of cancer but will never become clinically significant or cause death during the patient's remaining life span. This problem is compounded by the fact that the most common cancers appear most frequently at ages when competing causes of death are more frequent. Selection bias occurs because the population most likely to seek screening often differs from the general population to which the screening test might be applied. In general, volunteers for studies are more health conscious and likely to have a better prognosis or lower mortality rate irrespective of the screening result. This is termed the healthy volunteer effect.

Drawbacks of Screening Risks associated with screening include harm caused by the screening intervention itself, harm due to the further investigation of persons with positive tests (both true and false positives), and harm from the treatment of persons with a true positive result, whether or not life is extended by treatment (e.g., even if a screening test reduces relative cause-specific mortality by 15–30%, 70–85% of those diagnosed still go on to die of the target cancer). The diagnosis and treatment of cancers that would never have caused medical problems (i.e., overdiagnosis) can lead to the harm of unnecessary treatment (i.e., overtreatment) and give patients the anxiety of a cancer diagnosis. The psychosocial impact of cancer screening can be substantial when applied to the entire population.

Assessment of Screening Tests Good clinical trial design can offset some biases of screening and directly identify the balance of risks and benefits of a screening test. A randomized controlled screening trial with cause-specific mortality as the endpoint provides the strongest support for a screening intervention. Overall mortality should also be reported to detect an adverse effect of screening and treatment on other disease outcomes (e.g., cardiovascular disease, treatment-induced cancers). In a randomized trial, two like populations are randomly established. One is given the usual standard of care (which may be no screening at all) and the other receives the screening intervention being assessed. Efficacy for the population studied is established when the group receiving the screening test has a lower cause-specific mortality rate than the control group. Studies showing a reduction in the incidence of advanced-stage disease, improved survival, or a stage shift are weaker (and possibly misleading) evidence of benefit. These latter criteria are early indicators but not sufficient to definitively establish the value of a screening test. Although a randomized, controlled screening trial provides the strongest evidence to support a screening test, it is not perfect. Unless the trial is population-based, it does not remove the question of generalizability to the target population. Screening trials generally involve thousands of persons and last for years. Less definitive study designs are therefore used to assess the effectiveness of a screening test of proven efficacy in actual practice. However, every nonrandomized study design is subject to strong confounders. In descending order of strength, evidence may also be derived from the findings of internally controlled trials using intervention allocation methods other than randomization (e.g., allocation by birth date, date of clinic visit); the findings of analytic observational studies; or the results of multiple time series studies with or without the intervention.

Screening for Specific Cancers Screening for cervical, colon, and breast cancer has the potential to be beneficial for certain age groups. Although these tests can reduce deaths from the cancer being screened for, meta-analyses of randomized trials have not shown that they affect all-cause mortality. Lung cancer screening can also reduce deaths in specific settings, depending on age and smoking history. Special surveillance of those at high risk for a specific cancer because of a family history or a genetic risk factor may be prudent, but few studies have assessed the effect on mortality. A number of organizations have considered whether or not to endorse routine use of certain screening tests. Because their perspectives have varied, they have arrived at different recommendations. The American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) publish screening guidelines (Table 75-3); the American Academy of Family Practitioners (AAFP) often follows/endorses the USPSTF recommendations; and the American College of Physicians (ACP) develops recommendations based on structured reviews of other organizations' guidelines.

BREAST CANCER Breast self-examination, clinical breast examination by a caregiver, mammography, and magnetic resonance imaging (MRI) have all been variably advocated as useful screening tools. A number of trials suggest that annual or biennial screening with mammography in normal-risk women older than age 50 years decreases breast cancer mortality. In most, breast cancer-related mortality rates were decreased by 15–30%. Experts disagree on whether average-risk women age 40–49 years should receive regular screening. The U.K. Age Trial, the only randomized trial of breast cancer screening to specifically evaluate the impact of mammography in women age 40–49 years, found no statistically significant difference in breast cancer mortality for screened women versus controls after about 22 years of follow-up (relative risk 0.88; 95% confidence interval, 0.74–1.03); however, <70% of women received screening in the intervention arm, potentially diluting the observed effect. A meta-analysis of nine large randomized trials showed an 8% relative reduction in breast cancer mortality (relative risk 0.92; 95% confidence interval, 0.75–1.02) from mammography screening for women age 39–49 years after 11–20 years of follow-up. This is equivalent to 3 breast cancer deaths prevented per 10,000 women over 10 years (although the result is not statistically significant). At the same time, nearly half of women age 40–49 years screened annually will have false-positive mammograms necessitating further evaluation, often including biopsy. Estimates of overdiagnosis range from 10 to 50% of diagnosed invasive cancers. CHAPTER 75 Prevention and Early Detection of Cancer In the United States, widespread screening over the past several decades has not been accompanied by a reduction in incidence of metastatic breast cancer despite a large increase in early-stage disease, suggesting a substantial amount of overdiagnosis at the population level. In addition, the substantial improvements in systemic therapy have likely decreased the impact of mammography and early detection on falling breast cancer mortality rates. Digital breast tomosynthesis is a newer method of breast cancer screening that reconstructs multiple x-ray images of the breast into superimposed “three-dimensional” slices. Although some evidence is available concerning the test characteristics of this modality, there are currently no data on its effects on health outcomes such as breast cancer-related morbidity, mortality, or overdiagnosis rates. A large randomized trial comparing standard digital mammography to tomosynthesis is in progress. No study of breast self-examination has shown it to decrease mortality. A randomized controlled trial of approximately 266,000 women in China demonstrated no difference in breast cancer mortality between a group that received intensive breast self-exam instruction and reinforcement/reminders and controls at 10 years of follow-up. However, more benign breast lesions were discovered and more breast

biopsies were performed in the self-examination arm. Genetic screening for BRCA1 and BRCA2 mutations and other markers of breast cancer risk has identified a group of women at high risk for breast cancer. Unfortunately, when to begin and the optimal frequency of screening have not been defined. Mammography is less sensitive at detecting breast cancers in women carrying BRCA1 and

TABLE 75-3 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition
CANCER TYPE TEST OR PROCEDURE USPSTF ACS Breast Self-examination "D"b (Not in current recommendations; from 2009) Women, all ages: No specific recommendation Clinical examination Women ≥ 40 years: "I" (as a stand-alone without mammography) (Not in current recommendations;

from 2009) Mammography Women aged 40-74 years: Biennial screening

mammography ("B") Women ≥ 75 years: "I" Magnetic resonance imaging (MRI) "I" Women with $>20\%$ lifetime risk of breast cancer: Screen with MRI plus mammography annually Women with 15-20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually Women with $<15\%$ lifetime risk of breast cancer: Do not screen annually with MRI Cervical Pap test (cytology) Women <21 years: "D" Women 21-29 years: Screen with cytology alone every

3 years ("A") Women 30-65 years: Screen with cytology alone every

3 years, or with co-testing (HPV testing + cytology) every

5 years (two of three options, see HPV test below) ("A") Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous

causes: "D" PART 4 Oncology and Hematology HPV test Women <30 years: Do not use HPV testing for cervical cancer screening Women 30-65 years: Screen with HPV testing alone or in combination with cytology every 5 years (two of three options, see Pap test above) ("A") Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D" Colorectal Overall Adults 50-75 years: "A" Screen for colorectal cancer Adults 45-50 years: "B" Screen for colorectal cancer Adults 76-85 years: "C" Selectively offer screening for colorectal cancer; consider the patient's overall health, prior screening history, and preferences Sigmoidoscopy Every 5 years; modeling suggests improved benefit if performed every 10 years in combination with annual FIT Fecal occult blood testing (FOBT) Every year Adults ≥ 45 years: Every year Colonoscopy Every 10 years Adults ≥ 45 years: Every 10 years Fecal DNA testing At least every 3 years Adults ≥ 45 years: Every 3 years Fecal immunochemical testing (FIT) Every year Adults ≥ 45 years: Every year Computed tomography (CT) colonography Every 5 years Adults ≥ 45 years: Every 5 years Lung Low-dose CT scan Adults 50-80 years, with a ≥ 20 pack-year smoking history, still smoking or have quit within past 15 years, annually: "B" Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery

Women, all ages: Do not recommend Women 40-44 years: Provide the opportunity to begin annual screening Women 45-54 years: Screen annually Women ≥ 55 years: Transition to biennial screening or have the opportunity to continue annual screening Women ≥ 40 should continue screening mammography as long as their overall health is good and they have a life expectancy of

10 years or longer Women <21 years: No screening Women 21–29 years: Screen every 3 years
 Women 30–65 years: Screen with co-testing (HPV testing + cytology) every 5 years or cytology alone every 3 years

(see HPV test below) Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen Women <30 years: Do not use HPV testing for cervical cancer screening Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above) Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen Adults ≥45–75 years: Screen for colorectal cancer with either a high-sensitivity stool-based test or a structural (visual) examination (≥45 years, qualified recommendation; ≥50 years, strong recommendation). Adults 76–85 years: Individualize screening based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation). Adults >85 years: Discourage screening (qualified recommendation). Every 5 years Adults ≥45 years: Every 5 years Men and women, 50–80 years, with ≥20 pack-year smoking history, current or former smoker, annually: Discuss benefits, limitations, and harms of screening; offer smoking cessation counseling and connection to resources where relevant. Individuals with comorbid conditions that substantially limit life expectancy should not be screened. (Continued)

TABLE 75-3 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition
 CANCER TYPE TEST OR PROCEDURE USPSTF ACS
 Ovarian CA-125 Transvaginal ultrasound Women, all ages: “D” Women with a high-risk hereditary cancer syndrome:

No recommendation Prostate Prostate-specific antigen (PSA) Men 55–69 years: The decision to undergo periodic PSA-based screening should be an individual one. Men should have an opportunity to discuss the potential benefits and harms of screening with their clinician. Clinicians should not screen men who do not express a preference for screening (“C”) Men ≥70 years: “D” Digital rectal examination (DRE) No individual recommendation As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal exam. Skin Complete skin examination by clinician or patient Adults, all ages: “I” No guidelines aSummary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition. bUSPSTF lettered recommendations are defined as follows: “A”: The USPSTF recommends the service because there is high certainty that the net benefit is substantial; “B”: The USPSTF recommends the service because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; “C”: The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small; “D”: The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; “I”: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Table only includes final, not draft, recommendations, from the USPSTF. Abbreviations: ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force. BRCA2 mutations, possibly because such cancers occur in younger women, in whom mammography is known to be less sensitive. MRI screening may be more sensitive than mammography in women at

high risk due to genetic predisposition or in women with very dense breast tissue, but specificity may be lower. An increase in overdiagnosis may accompany the higher sensitivity. The impact of MRI on breast cancer mortality with or without concomitant use of mammography has not been evaluated in a randomized controlled trial.

CERVICAL CANCER The cervical cancer mortality rate has fallen substantially since the widespread use of the Pap smear. Screening guidelines recommend regular Pap testing for all women who have reached the age of 21 (before this age, even in individuals that have begun sexual activity, screening may cause more harm than benefit). The recommended interval for Pap screening is 3 years. In all cases, screening more frequently adds little benefit but leads to important harms, including unnecessary procedures and overtreatment of transient lesions. With the onset of sexual activity comes the risk of sexual transmission of HPV, the fundamental etiologic factor for cervical cancer. Beginning at age 30, guidelines also include HPV testing with or without Pap smear. The screening interval for women who test normal using this approach may be lengthened to 5 years. An upper age limit at which screening ceases to be effective is not known, but women age 65 years with no abnormal results in the previous 10 years may choose to stop screening. Screening should be discontinued in women who have undergone a hysterectomy with cervical excision for noncancerous reasons. Although the efficacy of the Pap smear in reducing cervical cancer mortality has never been directly confirmed in a randomized, controlled setting, a clustered randomized trial in India evaluated the impact of one-time cervical visual inspection and immediate colposcopy, biopsy, and/or cryotherapy (where indicated) versus counseling on cervical cancer deaths in women age 30–59 years. After 7 years of follow-up, the age-standardized rate of death due to cervical cancer was 39.6 per 100,000 person-years in the intervention group versus 56.7 per 100,000 person-years in controls.

COLORECTAL CANCER Digital rectal examination (DRE), stool-based testing (fecal occult blood testing [FOBT], fecal immunochemical tests [FITs], multitargeted stool DNA tests), blood-based testing (SEPT9), and optical testing (rigid and flexible sigmoidoscopy, colonoscopy,

(Continued) Currently, there are no reliable screening tests for the early detection of ovarian cancer. For women at high risk of ovarian cancer, it has not been proven that using transvaginal ultrasound or serum CA-125 lowers their chances of dying from ovarian cancer. Starting at age 50, men at average risk and with a life expectancy of ≥ 10 years should talk to a doctor about the uncertainties, risks, and potential benefits of screening. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. For men with more than one first-degree relative with prostate cancer diagnosed before age 65, have this talk starting at age 40. How often they are screened will depend on their PSA level.

CHAPTER 75 Prevention and Early Detection of Cancer computed tomography [CT] colonography) have been considered for colorectal cancer screening. DRE is not an effective colorectal cancer screening test and is not recommended by any medical organization. **Stool-Based Testing** A meta-analysis of five randomized controlled trials demonstrated a 22% relative reduction in colorectal cancer mortality after two to nine rounds of biennial FOBT at 30 years of follow-up; annual screening was shown to result in a greater mortality reduction in a single trial (a 32% relative reduction). However, only 2–10% of those with occult blood in the stool actually have cancer. The high false-positive rate of FOBT therefore leads to a large number of diagnostic follow-up colonoscopies. FITs have higher sensitivity for colorectal cancer than FOBT tests and have largely replaced FOBT in clinical practice. Limited evidence suggests FITs may not detect proximal colonic tumors at the same rate as distal ones. Multitargeted stool DNA testing (e.g., Cologuard) combines FIT with testing for altered DNA biomarkers that are shed into the stool. Although limited evidence demonstrates that it can have a

higher single-test sensitivity for colorectal cancer than FIT alone, its specificity is lower, resulting in a higher number of false-positive tests and follow-up colonoscopies. No studies have yet evaluated its effects on colorectal cancer incidence, morbidity, or mortality. Blood-Based Testing A blood test for the methylated SEPT9 gene associated with colorectal cancer is available. Case-control studies suggest that it has a lower sensitivity and specificity than the FIT stool test. It also is more costly, and it is not recommended as a first-line screening test. Optical Testing Two meta-analyses of five randomized controlled trials of sigmoidoscopy found an 18% relative reduction in colorectal cancer incidence and a 28% relative reduction in colorectal cancer mortality. Participant ages ranged from 50 to 74 years, with follow-up ranging from 6 to 13 years. Diagnosis of adenomatous polyps by sigmoidoscopy should lead to evaluation of the entire colon with colonoscopy. The most efficient interval for screening sigmoidoscopy is unknown, but an interval of 5 years is often recommended. Case-control studies suggest that intervals of up to 15 years may confer benefit; a randomized trial in the U.K. demonstrated colorectal cancer mortality reduction with one-time screening.

One-time colonoscopy detects ~25% more advanced lesions (polyps >10 mm, villous adenomas, adenomatous polyps with high-grade dysplasia, invasive cancer) than one-time FOBT with sigmoidoscopy; comparative programmatic performance of the two modalities over time is not known. Perforation rates are about 4/10,000 for colonoscopy and 1/10,000 for sigmoidoscopy. Debate continues on whether colonoscopy is too expensive and invasive and whether sufficient provider capacity exists to be recommended as the preferred screening tool in standard-risk populations. Some observational studies suggest that efficacy of colonoscopy to decrease colorectal cancer mortality is higher on the left side of the colon than the right.

CT colonography, if done at expert centers, appears to have a sensitivity for polyps ≥ 6 mm, comparable to colonoscopy. However, the rate of extracolonic findings of abnormalities of uncertain significance that must nevertheless be worked up is high (~5–37%); the long-term cumulative radiation risk of repeated colonography screenings is also a concern. LUNG CANCER Chest x-ray and sputum cytology have been evaluated in several randomized lung cancer screening trials. The most recent and largest ($n = 154,901$) of these, a component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, found that, compared with usual care, annual chest x-ray did not reduce the risk of dying from lung cancer (relative risk 0.99; 95% confidence interval, 0.87–1.22) after 13 years. However, it showed evidence of overdiagnosis associated with chest x-ray. Low-dose CT has also been evaluated in several randomized trials. The largest and longest of these, the National Lung Screening Trial (NLST), was a randomized controlled trial of screening for lung cancer in ~53,000 persons age 55–74 years with a 30+ pack-year smoking history. It demonstrated a statistically significant reduction of about 3 fewer deaths per 1000 people screened with CT compared to chest x-ray after 12 years. Harms include the potential radiation risks associated with multiple scans, the discovery of incidental findings of unclear significance, and a high rate of false-positive test results. Both incidental findings and false-positive tests can lead to invasive diagnostic procedures associated with anxiety, complications, and expense. The NLST was performed at experienced screening centers, and the balance of benefits and harms may differ in the community setting at less experienced centers. PART 4 Oncology and Hematology OVARIAN CANCER Adnexal palpation, transvaginal ultrasound (TVUS), and serum CA-125 assay have been considered for ovarian cancer screening. A large randomized, controlled trial has shown that an annual screening program of TVUS and CA-125 in average-risk women does not reduce deaths from ovarian cancer (relative risk 1.21; 95% confidence interval, 0.99–1.48).

Adnexal palpation was dropped early in the study because it did not detect any ovarian cancers that were not detected by either TVUS or CA-125. A second large, randomized trial used a two-stage screening approach incorporating a risk of ovarian cancer algorithm that determined whether additional testing with CA-125 or TVUS was required. At 14 years of follow-up, there was no statistically significant reduction in ovarian cancer deaths. The risks and costs associated with the high number of false-positive results are impediments to routine use of these modalities for screening. In the PLCO trial, 10% of participants had a false-positive result from TVUS or CA-125, and one-third of these women underwent a major surgical procedure; the ratio of surgeries to screen-detected ovarian cancer was approximately 20:1. In September 2016, the FDA issued a safety communication recommending against using any ovarian cancer screening test, including the algorithm for risk of the cancer.

PROSTATE CANCER The most common prostate cancer screening modalities are digital rectal exam (DRE) and serum PSA assay. An emphasis on PSA screening has made prostate cancer the most common nonskin cancer diagnosed in American males. This disease is prone to lead-time bias, length bias, and overdiagnosis, and substantial debate continues among experts as to whether screening should be offered unless the patient specifically asks to be screened. Virtually all organizations stress the importance of informing men about the uncertainty regarding screening efficacy and the associated harms. Prostate

cancer screening clearly detects many asymptomatic cancers, but men older than age 50 years have a high prevalence of clinically insignificant prostate cancers (about 30–50% of men, increasing further as men age). The ability to distinguish tumors that are lethal but still curable from those that pose little or no threat to health is limited, although evidence suggests multiparametric MRI may aid decision-making. Randomized trials indicate that the effect of PSA screening on prostate cancer mortality across a population is, at best, small. Two major trials have been published. The PLCO Cancer Screening Trial was a multicenter U.S. trial that randomized almost 77,000 men age 55–74 years to receive either annual PSA testing for 6 years or usual care. At 13 years of follow-up, no statistically significant difference in the number of prostate cancer deaths was noted between the arms (rate ratio 1.09; 95% confidence interval, 0.87–1.36). More than half of men in the control arm received at least one PSA test during the trial, which may have diluted a small effect. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was a multinational study that randomized ~182,000 men between age 50 and 74 years (with a predefined “core” screening group of men age 55–69 years) to receive PSA testing or no screening. Recruitment and randomization procedures, as well as actual frequency of PSA testing, varied by country. After a median follow-up of 15.5 years, a 20% relative reduction in the risk of prostate cancer death in the screened arm was noted in the “core” screening group. The trial found that 570 men (95% confidence interval, 380–1137 men) would need to be invited to screening, and 18 cases of prostate cancer detected, to avert 1 death from prostate cancer. There was an unexplained imbalance in treatment between the two study arms, with a higher proportion of men with clinically localized cancer receiving radical prostatectomy in the screening arm and receiving it at experienced referral centers. Screening must be linked to effective therapy to have any benefit. Two trials conducted after the initiation of widespread PSA testing did not find a substantial decrease in prostate cancer deaths in control arms of “watchful waiting” or monitoring (i.e., no curative treatment) compared to radical prostatectomy or radiation therapy. Prostate cancer-specific survival was very good (about 99%) and nearly identical at a median follow-up of 10 years. Treatments for low-stage prostate cancer, such as surgery and radiation therapy, can cause substantial morbidity, including impotence and urinary incontinence.

SKIN CANCER Visual examination of all skin surfaces by the patient or by a health care provider is used in screening for

basal and squamous cell cancers and melanoma. No prospective randomized study has been performed to look for a mortality decrease. Unfortunately, screening is associated with a substantial rate of overdiagnosis. MULTICANCER EARLY DETECTION TESTS Multicancer early detection (MCED) tests look for multiple biomarkers in blood that are either directly released or induced by cancer cells. One potential purpose of these tests could be to screen for multiple cancers at the same time in asymptomatic people. However, most of the evidence at present for these tests comes from people who have already been diagnosed with cancer (a fundamentally different population); additionally, no data are available on health outcomes associated with using MCED tests for cancer screening. ■ ■ FURTHER READING Fenton JJ et al: Prostate-specific antigen-based screening for prostate cancer: Evidence report and systematic review for the U.S. Preventive Services Task Force. JAMA 319:1914, 2018. Jonas DE et al: Screening for lung cancer with low-dose computed tomography: Updated Evidence report and systematic review for the US Preventive Services Task Force. JAMA 325:971, 2021. Kramer BS, Croswell JM: Cancer screening: The clash of science and intuition. Annu Rev Med 60:125, 2009. Lin JS et al: Screening for colorectal cancer: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 325:1978, 2021.

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