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PART II

Prevention, Detection, and Diagnosis

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CHAPTER

4

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Dynamics of Cancer Prevention

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INTRODUCTION

Over the past several decades, epidemiologic, basic, and clinical research has contributed to major developments in cancer prevention *science*. Although a large body of knowledge exists, we are limited in our ability to translate it into appreciable declines in nationwide cancer incidence and mortality rates for all cancers, and for all subpopulations. A coordinated effort to explore cancer risk reduction measures, through healthy lifestyle behaviors and medical interventions, is essential to establishing definitive prevention practice. This chapter presents an overview of principles, current practices, research, policy, special challenges, and responsibilities and opportunities for nurses in cancer prevention.

CANCER PREVENTION PRINCIPLES

The premise of cancer prevention is that carcinogenesis is a multiyear process that, in its early phases of development, can be reversed, arrested, interrupted, controlled, or at least delayed by instituting behavioral or environmental changes or by chemopreventive interventions. Implicit in this premise are the notions that (1) early phases and/or risk of carcinogenesis can be recognized and detected and that (2) implementing approaches that interfere with carcinogenesis can be less harmful or burdensome than not interfering.[1–3]

While a variety of theories of carcinogenesis have evolved over the past several decades, the multistep, multiyear nature of the process has not been disputed. The steps typically associated with carcinogenesis are identified as initiation, promotion, and progression (**Figure 4-1**); they are influenced by genetic and dietary factors as well as macroenvironmental and microenvironmental conditions (e.g., inflammation). *Initiation* occurs rapidly with exposure to a carcinogenic agent (e.g., nitrosamines in tobacco smoke, ionizing radiation, oncogenic viruses, chronic gastroesophageal refluxate), resulting in an irreversible alteration in the genotype of a cancer stem cell. During *promotion*, the cell acquires phenotypic characteristics of malignant cells, such as increased cell proliferation, disorganization, and morphological changes.[4,5] The promotion phase spans an extended period of time, up to 40 years in some cases. Reversibility is a key feature of this phase, providing an opportunity to intercept the process through an intervention such as chemoprevention.[2] Further carcinogenic exposure and multiple alterations to the cell microenvironment may lead to *progression*, the final phase of carcinogenesis. This phase occurs over a period of one

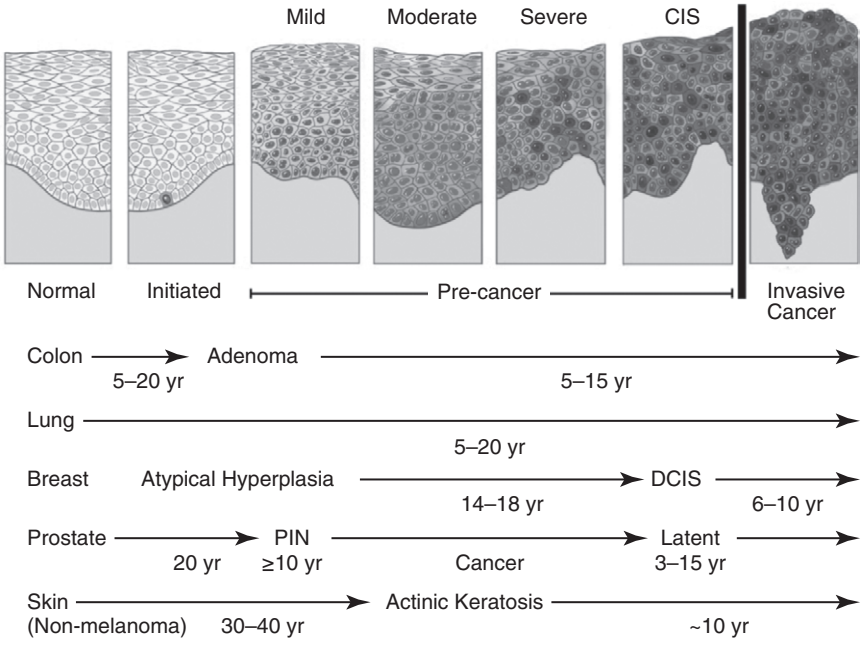

FIGURE 4-1

Carcinogenesis.
Abbreviations: CIS: carcinoma in situ; DCIS: ductal carcinoma in situ.

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or more years, is generally irreversible, and is characterized by progression of genetically altered cells to invasive malignancy.[6,7]

Although the steps of the carcinogenic process provide a framework for the development of common adult epithelial cancers,[8] a multitude of variations and overlaps exist within each phase and among different cancer types. Unraveling carcinogenesis is a central focus for cancer prevention researchers. Knowledge of genetic alterations and other processes that influence tumor development is critical for the purposes of early detection, risk stratification, and development of targeted therapeutics.[9]

Tumorigenesis requires not only the dysfunction of genetically damaged cells, but also a local tissue environment (termed the tumor microenvironment) that is conducive to their growth and survival. The tumor microenvironment is a complex dynamic network composed of a large number of cells that can be classified into four basic categories: (1) cells that can participate in tumor progression; (2) cells involved with forming the tumor vasculature; (3) cells of the innate and adaptive immune systems; and (4) cells that form the extracellular matrix (mesenchymal cells, or fibroblasts).[10] Continued expansion of tumor cells depends on whether ongoing interactions between those tumor cells and the other cells in the local tissue provide a survival advantage over normal cells.[11] In fact, it has become clear that the interactions between a tumor and its microenvironment occur at the earliest onset of disease.[12]

In light of its integral role in tumorigenesis, researchers are now looking at the tumor microenvironment as a potential target for cancer prevention strategies. Interfering with the production or function of cells that form the necessary supporting environment for cancer growth could be a key to preventing the onset of clinically significant cancers. Inflammatory mediators and immune cells are major players in the microenvironment and are of particular interest in current chemoprevention research as targets of modulation by aspirin and vaccines.[13,14] Likewise, biomarkers or indicators of the presence of the processes and components of the tumor microenvironment may improve our ability to identify susceptible individuals, so as to more accurately assess their risk and to predict their response to risk reduction measures.[15]

CANCER RISK

A basic tenet of cancer prevention is that the burden of the intervention must be proportionate to the level of risk. As discussed later, for those persons at average or relatively low risk, interventions that produce unwanted side effects or that are invasive, costly, time consuming, or long term in nature raise the risk/benefit ratio to unacceptable levels.[16] However, accurately determining cancer risk level, especially in asymptomatic individuals, is a formidable task except in rare cases such as familial syndromes, with exposure to some known carcinogen, and with some predisposing lesions. One of the goals of ongoing efforts to understand carcinogenesis and natural history is to uncover easily detectable characteristics that predict clinically meaningful risk.[17]

CANCER PREVENTION STRATEGIES

BEHAVIORAL AND LIFESTYLE INTERVENTIONS

Considerable evidence supports the proposition that lifestyle behaviors are responsible for approximately 70% of cancer deaths in the United States.[18,19] Understandably, efforts by the research community to investigate the effects of poor diet, physical inactivity, tobacco and alcohol use, infectious agents, obesity, and ionizing radiation on cancer incidence have flourished over the past several decades. In 2007, the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published the *WCRF/AICR Expert Report*, a comprehensive review of relevant evidence-based research evaluating lifestyle behaviors and cancer risk reduction.[20] The report is designed to function as a guide for future scientific research, educational programs, and, most importantly, global health policy. Overall, the report advocates increased physical activity, decreased alcohol intake, limited intake of processed foods, and ingestion of a healthy well-balanced diet as the source of a combination of bioactive cancer-preventive foods (**Table 4-1**).[20] In a follow-up to the initial report, the *WCRF/AICR Policy Report* was published in 2009. This document presents proposals for effective policies and programs targeting the overall improvement of health and specifically cancer prevention through lifestyle modifications. The *WCRF/AICR Policy Report* addresses action items for federal programs as well as individual citizens.[21]

The Continuous Update Project (CUP), a component of the WCRF/AICR, is an example of an ongoing scientific effort to evaluate evidence-based lifestyle behaviors and their specific effects on cancer risk reduction.[20,22] Recently, CUP published a report, *Diet, Nutrition, Physical Activity and Prostate Cancer*, which indicates that obesity is a key factor linked to increased risk for advanced prostate cancer.[23] Its analysis included 104 studies involving more than 9.8 million men and more than 191,000 cases of prostate cancer. The report joins others that have also linked excess body fat with an increased risk for development of cancers of the ovary, postmenopausal breast, colorectum, endometrium, esophagus, kidney, gallbladder, and pancreas.[24,25]

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TABLE 4-1

WCRF/AICR 2007 Recommendations for Decreasing Cancer Risk

General Dietary Recommendations
Be as lean as possible without becoming underweight.
Be physically active for at least 30 minutes every day.
Avoid sugary drinks.
Limit consumption of energy-dense foods.
Eat an increased variety of vegetables, fruits, whole grains, and legumes such as beans.
Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.
If consumed at all, limit alcoholic drinks to 2 per day for men and 1 per day for women.
Limit consumption of salty foods and foods processed with salt.
Do not use supplements to protect against cancer.
Special Population Recommendations
Breastfeed exclusively up to 6 months, then add other liquids and foods.
After treatment, cancer survivors should follow the recommendations for cancer prevention.

Source: Data from World Cancer Research Fund, American Institute for Cancer Research.[20]

Nutrition and Diet

Since the early 1980s, increased research efforts in biochemistry, epidemiology, molecular biology, and clinical research have explored the association between nutrition and cancer incidence. Numerous epidemiological (observational) studies have documented an association between diets rich in fruits and vegetables and a decreased risk for a variety of cancers (pharynx, larynx, lung, esophagus, stomach, cervix, uterus, colon, and rectum).

In contrast, clinical trials involving interventions with specific diets or nutritional agents have focused on evaluation of dietary supplements and global dietary modifications for their protective effects against cancer in a controlled setting. Ideally, observational studies should provide a rationale for evaluating a food component in clinical trials; however, clinical trial outcomes have not always supported the results from observational studies. As an example, the Polyp Prevention Trial (PPT) and the Wheat Bran Fiber Study (WBFS) were designed to validate findings from several large prospective observational studies that indicated an inverse relationship exists between increased fiber intake and colorectal cancer.[26,27] The PPT and WBFS evaluated the effect of diet on growth of new colorectal polyps in individuals with a prior history of polyp removal. Such clinical research investigating strategies for polyp prevention is an important avenue to pursue, as evidence shows 5% to 10% of polyps progress to malignancy if not removed.

The PPT, a 4-year study, randomized more than 2000 men and women to evaluate the effect of a high-fiber (18 g per 1000 calories), low-fat (20% of calories from fat), high-fruit/vegetable (3.5 servings per 1000 calories) diet on polyp recurrence. Although participants in the intervention group reported a significant increased intake of fiber, fruits, and vegetables and a reduced intake of fat, their risk for recurrent polyps was not significantly different from that of the control group. The PPT—Continued Follow-up Study (PPT-CFS) was initiated to provide an additional 4-year follow-up period to the original study.[28] Even with the extension, the PPT-CFS failed to show any protective effect of the diet on polyp recurrence and again showed persistent colorectal cancer risk despite frequent colonoscopy during PPT.[29]

Similarly, the WBFS randomized nearly 1500 men and women over three years to evaluate the effect of increased and decreased amounts of wheat bran fiber (13.5 g per day versus 2 g per day) for protective effects against recurrent colorectal polyps.[26] Once more, results were inconsistent with observational study results, as no benefit from dietary fiber was found. Individuals from both studies continue to be followed.

Another example of research related to dietary modification and cancer risk, the Women's Health Initiative (WHI), was a major trial sponsored by the National Institutes of Health (NIH), designed to evaluate cardiovascular disease, cancer, and osteoporosis in postmenopausal women over a 15-year period. Initiated in 1991, the WHI accrued nearly 162,000 generally healthy postmenopausal women. Two component studies of the WHI, the dietary modification (DM) clinical trial and the calcium and vitamin D (CaD)

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clinical trial, are directly related to diet and nutrition.[30–32] The DM trial randomized 48,835 females to examine strategies for preventing heart disease, as well as breast and colorectal cancers through changes in dietary patterns—specifically, low-fat intake, decreased total daily calories, increased fruit and vegetable consumption, and increased intake of grains. Results of the DM trial indicated that a low-fat diet did not significantly reduce the risk of breast or colorectal cancer in this cohort. In the CaD trial, 36,282 postmenopausal women were randomized to receive 1000 mg of calcium carbonate and 400 international units (IU) of vitamin D daily or a placebo.[31] The purpose of the study was to evaluate the effects of the supplements on risk for osteoporosis and colorectal cancer. Results indicated that supplemental intake of CaD did not decrease the incidence of colorectal cancer. In 2011, the CaD study was further evaluated for potential effects of calcium and vitamin D on total invasive cancer incidence and mortality. Results showed no decrease in either invasive cancer incidence or mortality.[33]

Clearly, major discrepancies have been found between observational studies and clinical trials evaluating associations between dietary modification and cancer risk. Instances of conflicting results between epidemiological and clinical trial research have been reported for other food products as well (e.g., selenium, folate, and carotenoids). Reasons for these discrepancies may be related to incomplete knowledge of mechanisms of the protective effects of individual nutraceuticals or aspects of trial design (e.g., self-reporting versus controlled clinical trial setting, baseline nutritional/nutrient status of trial participants). Alternatively, as suggested in a recent WCRF/AICR report,[20] a healthy well-rounded diet combining a wide array of nutrients throughout the life cycle may provide the best protective benefit, rather than inclusion or exclusion of any one individual nutrient.

Physical Activity

Obesity is an established risk factor for many cancers. Nearly 36% of adults and 20% of children in the United States are obese, defined as having a body mass index (BMI) of 30 kg/m^2 or greater.[21] The American Cancer Society (ACS) estimates that nearly 190,000 cancer deaths in the United States each year are attributable to poor diet and lack of physical activity.[34,35] Nutrition and diet are often studied in conjunction with physical activity, obesity, BMI, energy intake, and inflammation, with these factors being considered together in evaluating associations with cancer risk. The most recent ACS guidelines on nutrition and physical activity for cancer prevention, which are evidence based, were published in 2012.[35] The evidence base for guidelines for lifestyle behaviors poses specific challenges. The studies are limited by practical factors such as the fact that they cannot be blinded; they should be of long duration, which is often not the case; these studies begin later in life than is optimal for instituting preventive interventions; or follow-up is too short to reflect any benefit that might exist. Thus, guidelines are synthesized from a combination of shorter-term clinical trials and observational studies, along with an expanding body of knowledge about the biology of cancer.

While the evaluation of relationships between obesity, physical activity, and cancer are actively being pursued in observational studies and some clinical trials, recently more creative approaches have been evaluated in the context of social media. For example, a recent clinical trial randomized 134 undergraduate students to (1) a group with access to a physical activity-focused website along with a physical activity self-monitoring tool, and enrollment in a Facebook support group, or (2) an education-only control group with access to the same website.[36] Subjects in the intervention arm were encouraged by a communications moderator to engage in social support activities via a physical activity Facebook group. The primary endpoint was perceived social support for physical activity, while the secondary endpoint was self-reported physical activity. The study did not find differences between the groups with regard to the increased perceived social support. However, higher participant satisfaction with the Facebook group component of the study suggested that online social networks may be feasible formats for delivery of healthcare programs to young adults. Studies such as this indicate that behavioral interventions leveraging online networks have enormous potential to influence social support for individuals engaging in healthy lifestyle behavioral activities.

Smoking Cessation and Control

Tobacco is the most common cause of cancer in the United States and accounts for 90% of lung cancers.[37,38] Tobacco use is responsible for approximately 160,000 cancer deaths in the United States annually and nearly 225,000 new cases of lung cancer.[18] The overall five-year survival rate for individuals diagnosed with lung cancer is 16%.[39] Currently, an estimated 45 million American adults are habitual tobacco users, while another 45 million are former smokers.[40]

The identification of tobacco as a carcinogen reflects a major achievement for the field of cancer prevention. Epidemiological and experimental studies in the 1950s provided strong evidence supporting tobacco exposure as an etiological factor for lung cancer.[41,42] Efforts for tobacco control began with the publication of the first *Surgeon General's Report on Smoking and Health* in 1964.[43] Despite a large body of behavioral and scientific evidence linking smoking and cancer, however, tobacco use remains the leading cause of preventable death in the United States, and it is associated with an increased risk for at least 14 cancers: cancers of the nasopharynx, nasal cavity, lips, oral cavity,

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pharynx, larynx, lung, esophagus, pancreas, cervix, kidney, bladder, and stomach, as well as acute myeloid leukemia.[44]

Overall, cigarette consumption among American adults has been declining since the U.S. Surgeon General's report in 1964. This downward trend in cigarette consumption has led to a major reduction in lung cancer mortality rates for men. In contrast, mortality rates for women are just beginning to plateau after rising steadily for many years. This disparity between mortality trends for men and women can be explained by the fact that women started to smoke in large numbers 20 years later than men; similarly, the decrease in female smoking began to take place 20 years later. Lung cancer develops over a period of 20 years or more, explaining the differences in peak time-points for male/female mortality rates. With this in mind, mortality rates for women are anticipated to begin decreasing over the next decade.[18]

The harms associated with tobacco use extend beyond habitual and former tobacco users. In 2014, another U.S. Surgeon General's report, *The Health Consequences of Smoking—50 Years of Progress*, identified detrimental effects of secondhand smoke, also called sidestream smoke.[44] Secondhand smoke has been shown to increase the risk for lung cancer and coronary heart disease among nonsmoking adults. Approximately 35,000 cardiac-related deaths and 3000 lung cancer deaths occur annually among nonsmokers, a considerable portion of which are likely due to sidestream smoke.[38] Secondhand smoke causes damaging effects on young children, leading to a doubling of respiratory-related visits to emergency departments and a tripling of hospitalizations compared to children from nonsmoking homes.[45]

Teen smokers present a unique public health problem. Approximately 3200 adolescents (i.e., persons younger than age 18) begin using tobacco each day; 2100 will become habitual smokers, and up to half will ultimately die from tobacco-related causes.[46] With such alarming statistics, national, state, local, and school initiatives are under way to educate children of all ages about the dangers associated with tobacco. It is incumbent upon nurses to participate in the development, implementation, and evaluation of these antismoking initiatives.

Among current adult smokers, 80% report a desire to quit smoking and 70% have attempted to quit; however, the success rate remains low.[47] Although a number of smoking cessation interventions are being implemented, only a few have proved successful. Current interventions rely on a variety of behavioral and pharmaceutical approaches, including cessation recommendations from primary healthcare providers, group programs and classes, individual counseling sessions, pharmacologic interventions, media campaigns, and worksite and statewide cessation programs.[48] The most successful approaches for adult tobacco cessation result from increasing excise taxes on tobacco products, funding state and local cessation and abstinence programs adequately, implementing broad-based antismoking campaigns, and enacting comprehensive clean air and smoke-free laws.[48]

Traditional cigarettes work by burning tobacco to release nicotine-containing smoke to the user. Electronic cigarettes (e-cigarettes) present a novel method for nicotine delivery that is reportedly advantageous when compared to traditional cigarette usage. E-cigarettes, which were first developed in China in the early 2000s, work by heating liquid nicotine and converting it to a vapor or mist, which the user then inhales. E-cigarettes generally consist of three major components: a battery, which powers the e-cigarette; a vaporization chamber, which includes a hollow tube connected to a mouthpiece that houses electronic controls and an atomizer; and a cartridge containing liquid nicotine. When a user inhales through the mouthpiece, the atomizer is activated, converting the liquid nicotine into vapor.[49,50] Manufacturers and consumers claim that e-cigarettes provide for reduced chemical exposure, decreased smoking-related symptoms, and efficacy in smoking reduction and cessation greater than with conventional nicotine replacement therapies (NRTs). However, these products present new challenges and concerns to legislators, clinicians, and public health advocates. Remaining unanswered questions include regulatory responsibility (state versus federal legislation), product quality control, long-term studies on e-cigarettes, and quantifying usefulness in harm reduction.[49]

Genetics Associated With Smoking

The association of genetic factors with lung cancer risk is multifaceted, involving not only gene variants that modify the risk of developing lung cancer in the presence of tobacco use, but also variants that influence smoking behavior.[51,52] The importance of the latter category of gene variants is evident in the positive association between lung cancer risk and number of cigarettes smoked per day. Factors that increase the amount of smoking are expected to correlate with risk. Among such factors is the rate of nicotine metabolism: The faster nicotine is metabolized, the more cigarettes that must be smoked to maintain the given level in the circulation that delivers the desired psychopharmacologic effect.

The enzyme that metabolizes the majority of nicotine is cytochrome P450 2A6, or CYP2A6, and is coded for by the *CYP2A6* gene. In addition to the common version of this gene, *CYP2A6* exists in variant (polymorphic) forms in some people; some of the variants code for CYP2A6 enzymes that break down nicotine faster than normal. A high CYP2A6 enzyme activity, implying an underlying "high-activity" *CYP2A6* gene polymorphism, has been shown to correlate with increased smoking behavior. In individuals who have "low-activity" *CYP2A6* gene polymorphisms, nicotine is metabolized more slowly, which may result in smoking fewer cigarettes per day, leading

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inevitably to a lower risk of lung cancer. This situation is seen among Japanese populations, who, compared to Caucasians, metabolize nicotine more slowly and, as a result, smoke fewer cigarettes per day.[51] This lower level of smoking among Japanese is believed to contribute to their lower risk of developing lung cancer.

Another approach to exploring the relationship of nicotine to smoking behavior is seen in a study that focused on a cluster of genes (the *CHRN* genes) that encode receptors for the neuronal nicotinic acetylcholine receptor (AChR). Rather than examining the metabolic activity of a gene product, this study looked at potential associations between variants of the *CHRN* genes themselves and smoking susceptibility. Specific polymorphisms in the cluster of AChR genes that includes *CHRNA5–CHRNA3–CHRNB4* were shown to be associated with smoking quantity.[52]

Overall, it appears that smoking behavior is influenced by variant forms of genes that make proteins involved in nicotine metabolism (*CYP2A6* genes) and nicotine action at its receptor (*CHRN* genes). The downstream effect of these gene polymorphisms is expected, via their impact on quantity of smoking, to influence the risk of lung cancer.

Smoking Policy Changes

In 2009, President Barack Obama signed into law the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which places the tobacco industry under the direct authority of the Food and Drug Administration (FDA).[53] This historic legislation empowers the FDA to impose potentially strict new controls on the production, sales, and marketing of tobacco products. The FDA now has the ability to require reduced nicotine levels of tobacco products, administer product safety tests, and issue recalls if necessary. A new office within the FDA, the Center for Tobacco Products, will implement the statute's regulations. The main provisions of the Family Smoking Prevention and Tobacco Control Act include the following mandates:

- Crack down on tobacco marketing and sales to children and adolescents
- Require more prominent, more effective health warnings on tobacco products
- Require tobacco companies to disclose the contents of tobacco products, as well as changes in products and research about their health effects
- Ban terms such as "light" and "low-tar" that mislead consumers into believing that certain cigarettes are safer
- Strictly regulate all health-related claims about tobacco products to ensure they are scientifically proven and do not discourage current tobacco users from quitting or encourage new users to start
- Empower the FDA authority to require changes in tobacco products, such as the removal or reduction of harmful ingredients

MEDICAL INTERVENTIONS

Chemoprevention

The term "chemoprevention" refers to the use of natural or synthetic agents to interrupt the carcinogenic process, thereby preventing progression to invasive cancer.[1–3]

Agents Used in Chemoprevention

Although chemopreventive agents are often nutritionally based (derived from food compounds or supplements), food components ingested as part of a regular diet are not considered chemoprevention.[5] Rather, chemoprevention refers to compounds manufactured in pill, capsule, ointment, or liquid form and administered in prescribed doses at specified frequencies.[3] Unlike population-based lifestyle interventions (e.g., diet, exercise, tobacco cessation), the use of chemopreventive agents can be recommended only for individuals and subpopulations known to be at increased risk for developing a malignancy, to justify their exposure to potential expected or unexpected adverse events.

Development of chemopreventive agents is often juxtaposed against that of chemotherapeutic agents used for cancer treatment to illustrate their unique challenges, with the most important being that the risk/benefit ratio must be very low, with minimal toxicities, if a drug is to be indicated for healthy individuals at fairly low risk for cancer. Conversely, in a high-risk situation, more side effects may be acceptable.[3,9,16] For example, the relatively low level of use of tamoxifen, an approved breast cancer preventive agent for women at high risk for breast cancer, has been disappointing, but is considered the result of very low—but real—associated risk of thromboembolic events and uterine malignancy. Taylor et al.[54] reported their study, in which 48 of 89 women at high-risk for breast cancer who were made aware of the availability of a risk reduction drug raised the issue of taking the drug with their physicians. Most of those women (37/48) received their physician's recommendation against the drug; 3 women were recommended to take it, only one of whom decided to take the drug for breast cancer chemoprevention. The decision not to start tamoxifen was most frequently attributed to fear of adverse events (46.8%), followed by low perception of cancer risk (34%) and physician's advice (31.9%).

Currently, most chemopreventive agents are administered through participation in clinical trials. **Table 4-2** provides a list of some of the major large chemoprevention trials in humans.

Agents become candidates for clinical testing after having been identified through epidemiological, laboratory, or preclinical animal research. Promising agents are those that have demonstrated modulation of intermediate endpoint biomarkers (discussed later) in preclinical animal or laboratory models, or that have shown a cancer preventive effect

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TABLE 4-2

Selected Phase III Chemoprevention Clinical Trials

Clinical Trial	Target Organ	Protocol Design	*N*	Outcome
Beta-Carotene and Retinol Efficacy Trial (CARET)[54]	Lung	Four-arm study: (1) beta-carotene 30 mg and retinol 25,000 IU; (2) beta-carotene 30 mg alone; (3) retinol 25,000 IU alone; (4) placebo	18,314	28% increased incidence of lung cancer; 17% increased mortality in beta-carotene group
Alpha-Tocopherol, Beta-Carotene Prevention Trial (ATBC)[55]	Lung	Two-arm study: (1) alpha-tocopherol (vitamin E) 50 mg; (2) beta-carotene 20 mg	29,133	No reduction in lung cancer incidence with alpha-tocopherol; 18% increased incidence of lung cancer and 8% increased lung cancer mortality rate in beta-carotene group
Breast Cancer Prevention Trial (BCPT)[56]	Breast	Two-arm study: (1) tamoxifen 20 mg; (2) placebo	13,388	49% reduction in breast cancer incidence in tamoxifen group
Prostate Cancer Prevention Trial (PCPT)[57]	Prostate	Two-arm study: (1) finasteride 5 mg; (2) placebo	18,822	25% reduction of prostate cancer in finasteride arm
Nutritional Prevention of Cancer (NPC)[58]	Second primary cancers in people with history of previous skin cancer	Two-arm study: (1) selenium 200 μg; (2) placebo	1312	Increase in both basal and squamous cell skin cancer in selenium arm
Nutritional Intervention Studies of Esophageal Cancer (Linxian, China)[59]	Esophageal cancer	Four-arm study: (1) oral vitamin C/molybdenum; (2) beta-carotene, vitamin E, selenium; (3) retinol; (4) riboflavin, niacin	30,000	Beta-carotene, selenium, vitamin E group experienced lower esophageal cancer incidence and mortality
Adenoma Prevention with Celecoxib Trial (APC)[60]	Colorectal adenoma	Three-arm study: (1) 200 mg celecoxib bid; (2) 400 mg celecoxib bid; (3) placebo twice daily (in individuals with familial adenomatous polyposis)	2035	33% reduction in adenoma recurrence and advanced adenoma recurrence in participants who took celecoxib daily for 3 years compared to placebo
Women's Health Study[61]	All cancers by site; cancer mortality by site	Four-arm study: (1) 600 IU of vitamin E on alternate days; (2) 100 mg of aspirin on alternate days; (3) 600 IU of vitamin E and 100 mg aspirin on alternate days ; (4) placebo	39,876	No overall benefit for cancer or cancer mortality in healthy women; small nonsignificant reduction in lung cancer incidence in the aspirin group
Selenium and Vitamin E Cancer Prevention Trial (SELECT)[62]	Prostate	Four-arm study: (1) vitamin E alone; (2) vitamin E and selenium; (3) selenium alone; (4) placebo	35,000	Selenium and vitamin E supplements, taken either alone or together, did not reduce the incidence of prostate cancer
Study of Tamoxifen and Raloxifene (STAR)[63]	Breast	Two-arm study: (1) tamoxifen 20 mg; (2) raloxifene 60 mg	19,747	Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer

in observational studies. Most agents that are being tested in chemoprevention clinical trials have been used for other clinical indications and have an established safety profile, leading them to be termed "repurposed" drugs.[64]

Clinical testing entails a well-defined clinical trials process. Although many agents enter clinical trials, few progress successfully to definitive phase III randomized controlled trials (RCTs), and fewer still find their way into standard medical practice. Currently, only 12 chemopreventive agents have received approval from the FDA for standard use in cancer risk management: five agents for treatment of the premalignant lesion actinic keratosis, two for superficial bladder cancer recurrence, two for breast cancer risk reduction, two vaccines to prevent HPV infection and thereby anal and genital cancer, and one agent for ablation of high-grade Barrett's esophagus (**Table 4-3**).[65–75]

TABLE 4-3

FDA-Approved Chemopreventive Agents

Agent	Cohort	Agent Route and Schedule	Adverse Events	Indication
*†Tamoxifen[66] Initially approved for treatment of breast cancer	• Females: Age 35 years or older • DCIS after breast surgery and radiation with no prior diagnosis of breast cancer • At increased risk for the disease with 5-year projected absolute risk ≥ 1.66%, per NCI Breast Cancer Risk Assessment Tool or with LCIS	Oral daily × 5 years	Mainly in women > 50 years old: • Endometrial cancer • Stroke • Pulmonary emboli • DVT • Cataracts • Menopausal symptoms	• Reduce risk of invasive breast cancer in women with DCIS • Reduce risk of breast cancer
*†Raloxifene[75] Initially approved for osteoporosis	• Postmenopausal females • At high risk for invasive breast cancer • ≥ 1 breast biopsy LCIS or • Atypical hyperplasia • ≥ 1 first-degree relatives with breast cancer, • 5-year risk of breast cancer ≥ 1.66% as per the modified Gail model	Oral daily × 5 years	• Stroke • Pulmonary emboli • DVT	Reduce risk of invasive breast cancer
†HPV bivalent (types 16 and 18) vaccine, recombinant (Cervarix)[65]	Females: Ages 9–25 years	IM injections Series of 3 at 0, 2, 6 months	• Local injection-site reactions • Headache • Fever	• Prevent cervical cancer • Prevent CIN 2 or higher • Prevent cervical adenocarcinoma in situ • Prevent CIN 1 caused by HPV 16 and 18

†HPV quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant Gardasil[67]	Females: Ages 9–26 years	IM injections
		Series of 3 at 0, 2, 6 months
			• Local injection-site reactions
			• Nausea
			• Dizziness
			• Vomiting
			• Syncope
				• Prevent cervical, vulvar, and vaginal cancer
				• Prevent following diseases caused by HPV 6, 11, 16, and 18:
				  • Cervical cancer
				  • Genital warts
				  • Following precancerous or dysplastic lesions:
				  • Cervical AIS
				  • CIN 1, 2 and 3
				  • VIN 2 and 3
				  • VaIN 2 and 3
				• Anal cancer
				• Anal in situ

(continues)

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TABLE 4-3

FDA-Approved Chemopreventive Agents (*continued*)

Agent	Cohort	Agent Route and Schedule	Adverse Events	Indication
*†BCG[74] Initially approved for percutaneous use of vaccine for tuberculosis	Males and females Diagnosed with CIS of the urinary bladder	Intravesical instillation via urinary catheter • Q week × 6 • +/− monthly × 6–12 months or • +/− every 3–6 months × 2 years	• For 2 days, rarely longer • Frequency • Dysuria • Hematuria • Abdominal pain	• Treat and prevent CIS of urinary bladder • Prevent primary or recurrent papillary tumors after TUR • Stage Ta and/or T1 • Stage TaG1 papillary tumors if high risk of recurrence
†Valrubicin[71]	Males and females BCG-refractory CIS of the urinary bladder when immediate cystectomy not indicated	Intravesical instillation via urinary catheter	• Frequency • Dysuria • Hematuria • Abdominal pain	Treat CIS of the urinary bladder when immediate cystectomy is associated with unacceptable morbidity/mortality
*PDT with porfimer sodium[72] Initially approved for treatment of obstructions due to non-small cell lung and esophageal cancer	Males and females With HGD in Barrett's esophagus	IV porfimer on day 1 Endoscopic laser days 3 and 5	• Photosensitivity < 3 months • Esophageal strictures • Vomiting • Noncardiac chest pain • Pyrexia • Dysphagia • Constipation • Dehydration • Nausea • Hiccups	Treat HGD in Barrett's esophagus when esophagectomy is not indicated
*Diclofenac with hyaluronic acid[73] Initially approved for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis	Males and females with AK	Topical BID × 3 months	• Local skin reactions • Erythema • Edema • Pruritus • Rash	Treat AK
*Fluorouracil[70] Initially approved for IV administration for treatment of multiple epithelial cancers	Males and females with AK	Topical BID until clear up to 12 weeks	• Local skin reactions • Erythema • Crusting/erosions	Treat AK

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*Imiquimod[68,69] Initially approved for genital and perianal warts	Males and females with AK	Topical QD: 2-week cycles until clear or 2–3 days per week up to 4 months	• Local skin reactions • Erythema • Edema • Pruritus • Weeping • Excoriation • Flu-like symptoms	Treat AK
Ingenol mebutate[68]	Males and females with AK	Topical × 2–3 days	• Local reaction • Erythema • Edema • Pruritus • Nasopharyngitis • Headache • Periorbital edema • Local infection	Treat AK (face, scalp, trunk, extremities)
5-aminolevulinic acid and methylaminolevulinate with PDT[69]	Males and females with AK	Topical with light therapy	During illumination • Local skin reaction • Erythema • Edema • Blister • Crusting • Mild to moderate pain	Treat AK

With more serious toxicity, the indicated patient cohort is more restricted in whom benefits will outweigh risks.

*Chemopreventive agents that have been previously FDA-approved for another indication.

†Agents that are approved with a cancer prevention or cancer risk reduction indication rather than treatment of premalignant lesions.

Abbreviations: AIS: adenocarcinoma in situ; AK: actinic keratoses; BCG: Bacillus Calmette-Guérin; CIN: cervical intraepithelial neoplasia; CIS: carcinoma in situ; DCIS: ductal carcinoma in situ; DVT: deep vein thrombosis; FDA: Food and Drug Administration; HGD: high grade dysplasia; HPV: human papillomavirus; IM: intramuscular; IV: intravenous; LCIS: lobular carcinoma in situ; NCI: National Cancer Institute; PDT: photodynamic therapy; TUR: transurethral resection; VaIN: vaginal intra-epithelial neoplasia; VIN: vulvar intraepithelial neoplasia.

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A selective cyclooxygenase-2 (COX-2) inhibitor received conditional and accelerated approval in 1999 for the reduction of colorectal adenomas in high-risk individuals with familial adenomatous polyposis (FAP). However, approval was voluntarily withdrawn in 2011 by the drug manufacturer, not due to any new efficacy or safety data, but rather for not having met the requirement of postmarketing verification of clinical benefit (i.e., favorable risk/benefit ratio).[76] As shown in Table 4-3, the approved agents exemplify the required inverse correlation between burden of the drug (i.e., administration and toxicity) and cancer risk level of the intended patient population. Most of the agents are also examples of repurposed medications, having been previously approved for other indications. The table also indicates which agents are explicitly approved for cancer prevention versus treatment of intraepithelial neoplasia.

Chemopreventive agents are assessed for activity, safety, and efficacy in a series of phased trials, similar to chemotherapy treatment trials (**Table 4-4**). Once the safety and efficacy of a candidate agent have been established, the agent is evaluated in long-term phase III RCTs for its ability to decrease cancer incidence. Given the rarity of cancer occurrence even among high-risk individuals, by nature these studies using cancer incidence as the primary endpoint are costly, must accrue hundreds or thousands of participants, and generally take many years to complete.

In 2006, the FDA introduced the concept of exploratory investigational new drug (IND) studies, also called phase 0 studies or microdosing studies. The purpose of phase 0 studies is to shorten the clinical trials timeline, in part by limiting the number of subjects required for testing. Phase 0 studies evaluate agents for pharmacokinetic (what the body does to the drug—distribution in body tissue and elimination of drug) and pharmacodynamic (what the drug does to the body—modulating biomarkers in body tissues and fluids) activity. Importantly, phase 0 studies address the ability of the agent to modulate a molecular target through administration of a one-time, subtherapeutic dose administered to a small number of subjects (10–15). If an agent exhibits the ability to modulate the target, it may be selected to advance to an accelerated phase I or IIa trial.

Biomarkers Used in Chemoprevention

In cancer prevention research, biomarkers refer to substances in body tissues or fluids that are indicative of biological events that occur during the process of carcinogenesis. The actual substances that comprise biomarkers include genes, RNAs, proteins, and metabolites. Even characteristic histologies associated with benign lesions can serve in some cases as biomarkers.

The molecular changes that occur during tumor development often take place over a number of years, especially in the common adult epithelial cancers. Because of this lengthy period of carcinogenesis, biomarkers can serve a number of purposes: detecting cancers early; determining prognosis; predicting and monitoring therapeutic response to given agents; monitoring disease progression; and identifying individuals at increased risk of specific cancers. In their capacity of assessing drug response, biomarkers are

TABLE 4-4

Phases of Cancer Chemoprevention Clinical Trials

Trial Phase	Main Goal	Main Characteristics
Phase 0 (exploratory)	Assess molecularly targeted agents for proof-of-concept to determine whether further clinical development is warranted	Limited duration; agent microdose administered one time for pharmacokinetic and pharmacodynamic activity; performed in small number of subjects (10–15); no possibility of therapeutic benefit
Phase I	Assess dose-related agent safety and toxicity in preparation for more advanced clinical testing	Short duration; performed in small number of subjects
Phase II	Test biological activity and efficacy of agent specific to a premalignant condition	Short duration; performed in a small number of subjects; often measured against biomarkers along the carcinogenesis continuum
Ia	Test agent efficacy *without* placebo controls in cases where safety has been established through prior use or testing	Assess feasibility of using the agent; agents meeting criteria may bypass phase I testing and advance directly into phase IIa
Ib	Test agent efficacy *with* placebo controls in cases where safety of agent has been established through prior use or testing	Assess feasibility of using the agent; agents may bypass phase I testing and advance directly into phase IIb
Phase III	Test agents in randomized, placebo-controlled trial designed for a specific indication	Long duration; randomized clinical trials requiring large numbers of participants

Source: Data from Richmond and Viner.[77]

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considered surrogates for presumed definitive clinical endpoints (e.g., cancer incidence, cancer-related mortality).[78]

Early Detection Biomarkers. To be useful for early detection/screening, biomarker tests must accurately distinguish patients with cancer from those without cancer and be minimally invasive, cost-effective, and acceptable to patients and physicians.[78] The Early Detection Research Network (EDRN) is a National Cancer Institute (NCI)–run program to develop and validate biomarkers for screening as well as other applications. Currently, more than 300 biomarkers for most of the major adult epithelial cancers are in various phases of development and validation. For prostate cancer, for example, assays are being developed for gene rearrangements, including the *TMPRSS2-EST* gene fusions where a portion of *TMPRSS* is fused to a portion of an *EST* family gene. Other biomarkers that are being developed for prostate cancer include RNA PCA3 (an RNA that does not code for protein), the proteins proPSA and CD90, and autoantibodies. Biomarkers for colon cancer include mutations in the oncogene *K-ras*, as well as other gene mutations and epigenetic markers in both stool and urine, and proteins CCSA-2 and CCSA-3 in blood. Biomarkers for ovarian cancer include the proteins MIF-1 and osteopontin in blood.

EDRN is working toward validating a few biomarkers, such as autoantibodies against annexins and PGP9.5 for lung cancer and the proteins DCP and AFP-L3 for liver cancer.[79,80] Five biomarkers developed through the EDRN are either approved or pending approval by the FDA: proPSA in blood for prostate cancer; PCA3 in urine for prostate cancer; OVA1TM for ovarian cancer; ROMA algorithm for CA125 and HE4 tests for pelvic mass malignancies; and DCP and AFP-L3 for hepatocellular carcinoma in blood.[80]

Surrogate Endpoint Biomarkers/Intermediate Endpoint Biomarkers. The traditional endpoint for establishing chemopreventive efficacy of an agent in large phase III RCTs is cancer incidence. Although statistics for cancer incidence and mortality in the general population might appear high, the risk of any one individual developing malignant disease is relatively low. Cancer incidence is therefore relatively rare, requiring large numbers of study subjects, long duration of time for follow-up, and costly investments for incidence to be used as an endpoint in prevention studies. Consequently, it is not an appropriate endpoint for earlier-phase studies of short duration and with limited accrual.

The use of biomarkers as intermediate endpoints plays an important role in early-phase chemoprevention clinical trials; the purpose served by these biomarkers is to predict cancer occurrence.[81,82] An intermediate endpoint biomarker, also called a surrogate endpoint biomarker, is a marker representing a biological event that takes place (i.e., is "intermediate") between carcinogenic initiation and progression to invasive malignancy.[81,83] To be useful, a surrogate/intermediate endpoint biomarker must be reliable, highly sensitive and specific, quantitative, easily obtained from study participants, part of the causal pathway for disease, capable of being modulated by a test agent, and have high predictive value for the disease (cancer occurrence).[83] Intermediate endpoints may take the form of grossly visible lesions, some of which are considered premalignant lesions; examples include oral leukoplakia, colon polyps, and dysplastic nevi. Alternatively, lesions that are visible only at the histological level, such as hyperplasia, metaplasia, and dysplasia, can serve as intermediate endpoint biomarkers. Biochemical markers, including enzymes such as ornithine decarboxylase and prostaglandin synthetase, can also function as intermediate biomarkers. In addition, genetic abnormalities, such as DNA ploidy, oncogene activation/suppression, and micronuclei can be used for this purpose.

Cancer Risk Biomarkers. Biomarkers that serve to establish an individual's increased risk of developing a specific cancer are called risk biomarkers.[78] These biomarkers are, for the most part, premalignant lesions. For example, a breast biopsy that shows atypical ductal hyperplasia indicates that a female is at increased risk of developing breast cancer, just as colorectal adenomas are associated with an increased risk of colon cancer and oral leukoplakia is associated with an increased risk of developing oral cancer. An important aspect of risk biomarkers is that they can be used to identify potential participants for chemoprevention clinical trials.[84] A caveat in assessing cancer risk is that screening for risk in normal subjects must utilize minimally invasive techniques that are highly specific, sensitive, and quantitative.

Chemoprevention Cohorts

Chemoprevention studies target only individuals at increased risk for developing a specific cancer; they are not appropriate for individuals of average risk in the general population. Increased risk refers to individuals with personal or family history of the disease, known exposure to a carcinogen, or history of a prior malignancy. Studying such homogeneous increased-risk cohorts allows researchers to attain statistical significance with smaller sample sizes and shorter observation periods, since an increased number of cancer events are anticipated in this group. As an example, lung cancer chemoprevention studies target smokers or former smokers, since tobacco exposure is known to increase the incidence of the disease. But again, the risk of any individual smoker is still quite low (only 20% of smokers develop lung cancer); consequently, 1000 or more individuals may have to be screened to observe 100 lung cancer cases.

Recruitment of appropriate subjects to clinical trials is a major challenge for researchers. Although only 5% of adult oncology patients participate in therapeutic trials, the estimated participation of eligible individuals in prevention trials is far less. Unlike treatment trials, prevention studies

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TABLE 4-5

Characteristics of Chemoprevention and Chemotherapy Clinical Trials

	Chemoprevention Trials	Chemotherapy Trials
Goals	Cancer prevention: decrease cancer incidence and mortality; prevent or reverse premalignant lesions; prevent second primary cancers	Cancer treatment: increase chance of cure or remission; decrease mortality and morbidity
Cohorts	Individuals without cancer; high-risk populations; individuals with premalignant lesions; previously treated for malignancy, but currently disease free	Individuals with cancer
Biomarkers	Intermediate/surrogate endpoint biomarkers; early detection biomarkers; cancer risk biomarkers	Cancer eradication; cancer control; cancer palliation
Agents	Minimal toxicity profile; potentially long-term administration	Moderate to high toxicity profile is tolerated; relatively short-term administration

enroll relatively healthy individuals. Patients with cancer may be willing to tolerate moderate- to high-level toxicities associated with an investigative drug if the possibility of a cure exists. In contrast, high-risk but healthy individuals have a lower tolerance for even minor ongoing toxicities—for example, hot flashes, and arthralgias. **Table 4-5** summarizes characteristics of chemoprevention and chemotherapy clinical trials.

Recruitment of minority and underserved populations in prevention trials has posed a major challenge. Increased efforts at such recruitment in research have been an important focus of the NIH since the Revitalization Act was passed by the U.S. Congress in 1993, requiring inclusion of minorities and women in federally funded trials. The NIH established the National Center on Minority Health and Health Disparities (NCMHD) to coordinate research aimed at improving healthcare outcomes in underserved populations, where "underserved" refers to specific racial and ethnic groups, populations with lower socioeconomic status (SES), women, and elderly persons. The barriers to clinical trial participation by underserved populations reflect multilayered issues involving poor access to health care, discomfort with establishment medicine, and lack of education, as indicated in the recent literature. Interestingly, low SES has been identified as a greater barrier to healthcare and research opportunities than either race or ethnicity. Strategies to overcome these barriers to participation in clinical trials and enhance recruitment have been developed, but few have been validated.[85]

Chemoprevention Clinical Trials

Breast Cancer Prevention Trials

The class of drugs known as selective estrogen receptor modulators (SERMs) includes agents that bind to the estrogen receptor (ER) and either inhibit or activate ER action depending on the tissue type. In the breast, activation of the ER leads to cell proliferation of normal as well as cancerous breast cells. SERMs inhibit ER action in this tissue, leading to anticancer effects in the breast. The SERM tamoxifen has long been used to treat advanced and early-stage breast cancers that express the ER (ER-positive cancers).

The Breast Cancer Prevention Trial (BCPT), which was sponsored by the NCI's Division of Cancer Prevention (DCP) and conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), was a double-blind RCT evaluating the effectiveness of tamoxifen for breast cancer prevention in high-risk women. "High risk" for purposes of this trial was defined as a probability of 1.67% or greater of developing breast cancer over the next five years. Factors conferring high risk, primarily determined according to the Gail model, included age 60 or older or age 35–59 with a risk equal at least to that of an average 60-year-old; family history of breast cancer; history of benign breast disease; and hormonal functions, such as those associated with early age at menarche, late age at menopause, nulliparity, and late age at time of first birth. Tamoxifen, a SERM, was chosen for evaluation because of its antiestrogen activity in reducing the risk of breast cancer by blocking the effects of estrogen on breast tissue. The study accrued more than 13,000 participants between 1992 and 1997.[66] Subjects were randomized to receive tamoxifen 20 mg/day or placebo over a five-year period.

In the BCPT, women in the tamoxifen group experienced 49% fewer diagnoses of invasive and noninvasive breast cancer (e.g., ductal or lobular carcinoma in situ [DCIS or LCIS]) compared to the placebo group. Based on these findings, in October 1998 tamoxifen became the first drug ever to gain FDA approval for cancer risk reduction, establishing it as an effective medical intervention for breast cancer prevention in high-risk women.

Although the majority of adverse events associated with tamoxifen were temporary (hot flashes, vaginal dryness), several long-term and serious types of risks were identified,

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including increased incidence of endometrial cancer and several thromboembolic events (pulmonary embolism, deep vein thrombosis, and stroke). In 2005, after seven additional years of follow-up, the BCPT researchers reported that women in the tamoxifen group continued to experience a decreased incidence of invasive and noninvasive breast cancer at similar rates as in the original report. This group also continued to show increased rates of endometrial cancer and thromboembolic events at a similar rate to that reported earlier. All endometrial cancers in the tamoxifen-exposed group were stage I and, therefore, could be treated and "cured" with hysterectomy. In an overview of the outcomes of the four large tamoxifen versus placebo prevention trials, Cuzick et al.[86] reported an overall 38% reduction in invasive breast cancer incidence with tamoxifen.

Recent results from the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial in 6846 women with ER-positive breast cancer are informative regarding the preventive use of tamoxifen. In this treatment trial, extending tamoxifen to 10 years rather than stopping at the usual 5 years of adjuvant therapy resulted in a further reduction in recurrence and mortality, especially after year 10.[87] Based on these outcomes, serious consideration should be given to lengthening the duration of preventive tamoxifen therapy to a 10-year period.

Prompted by the serious risks associated with tamoxifen, the Study of Tamoxifen and Raloxifene (STAR) trial was designed to determine whether raloxifene, a second-generation SERM, was as effective as tamoxifen in reducing breast cancer incidence, but with fewer serious adverse events. STAR enrolled 19,747 postmenopausal high-risk women from 1999 to 2004. Eligibility for this study was restricted to postmenopausal women because raloxifene had previously been approved by the FDA for treatment of osteoporosis in this population. At a median follow-up of 47 months, nearly 50% risk reduction for invasive breast cancer was found in both groups, but women receiving raloxifene experienced 36% fewer uterine cancers and 29% fewer thromboembolic events than women receiving tamoxifen.[75] In a subsequent analysis at a median follow-up of 81 months published in 2010, results demonstrated that now the risk of invasive cancer was 24% higher with raloxifene compared to tamoxifen; thus, long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive breast cancer.[88] The reduction in endometrial cancer with raloxifene versus tamoxifen, which was not significant in the first results, now became significant (risk ratio [RR], 0.55; $p = 0.003$). Based on the STAR trial's results, the FDA approved raloxifene for risk reduction of breast cancer.

Cuzick et al.[89] published an updated meta-analysis of SERMs including 83,399 women from the four tamoxifen trials and a series of raloxifene trials with primary endpoints other than cancer—namely, osteoporosis and cardiac disease. Their overall finding was a 38% reduction in breast cancer incidence with the SERM, with a larger reduction in the first 5 years of follow-up (42%) than in years 5–10 (25%). Clearly, SERMs are effective in reducing the risk of breast cancer.

Continuing concerns about SERMs' toxicities and efficacy that is limited to only the subset of ER-positive cancers led to investigation of a second class of antiestrogen agents, aromatase inhibitors (AIs). Unlike SERMs, which inhibit the action of estrogen, the AIs actually deplete the body of estrogen by inhibiting the enzyme that makes it—that is, aromatase. The three third-generation AIs—anastrozole, letrozole, and exemestane—have all been shown to be superior to tamoxifen and, therefore, are approved for treatment of various stages of existing ER-positive breast cancer, but only in postmenopausal women. Their success in the adjuvant treatment setting for early-stage breast cancer, especially their suppression of new primary cancers in the opposite, or contralateral, breast, led to the testing of AIs for primary prevention in high-risk, postmenopausal women. Two large phase III trials have been completed using two of the AIs for prevention.

The NCI Canada sponsored the Mammary Prevention 3 (MAP-3) trial, which randomized 4560 postmenopausal women (median age: 62.5 years) who were at increased risk of breast cancer (median risk level: 2.3%) to the steroidal AI exemestane ($n = 2285$) versus placebo ($n = 2275$).[90] At a median follow-up of 35 months, 43 breast cancers were observed, 11 in the exemestane arm and 32 in the placebo arm, giving a hazard ratio (HR) of 0.35 ($p = 0.002$) and favoring exemestane. Only ER-positive breast cancers were reduced—7 with exemestane versus 27 with placebo (HR, 0.27; $p < 0.001$). Both invasive and in situ breast cancers were reduced with exemestane versus placebo (HR, 0.47; $p = 0.004$). No significant differences in adverse events were noted between the arms, and during a 3-year follow-up period only minimal changes in health-related quality-of-life were reported.

The MAP-3 findings are promising, as they are derived from the first definitive study to address the effect of an AI as a primary preventive intervention for breast cancer in high-risk women. Yet, several caveats must be considered in evaluating the outcomes.[91] Most important is the short duration of follow-up, 35 months, and the lack of maturity of the data. This limitation leaves open questions of long-term toxicity as well as the impact of noncritical but bothersome side effects, such as hot flashes, musculoskeletal events, and fatigue, on compliance. In addition, the median age of the women in the MAP-3 trial was 62.5 years, suggesting that a large proportion of the participants were at increased risk because they satisfied the 60-year minimum age requirement when no other risk factors were present. Overall, the MAP-3 population was at a relatively low level of increased risk and might not reflect women who would

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benefit most from a preventive intervention. Another key weakness in MAP-3 was the failure to incorporate prospectively into the study design a systematic reporting of critical bone endpoints, including new-onset osteoporosis and fractures. Nevertheless, the MAP-3 findings bring to the forefront the promise of AIs for breast cancer risk reduction.

A second AI, the nonsteroidal drug anastrozole, was tested for breast cancer prevention in the phase III International Breast Intervention Study II (IBIS-II). In this trial, 3864 postmenopausal women aged 40–70 years who were at high risk of breast cancer according to the Tyrer-Cuzick model[92] were randomized to anastrozole ($n = 1920$) or placebo ($n = 1944$).[66] After a median follow-up of 5 years, 2% ($n = 40$) of the women taking anastrozole developed breast cancer (either invasive breast cancer or DCIS) compared to 4% ($n = 85$) of women taking placebo (HR, 0.47; $p < 0.0001$), a result favoring the AI. This reduction in breast cancer risk with anastrozole surpassed that exhibited by tamoxifen in phase III RCTs (49% in NSABP P-1[56] and 38% in the overview).[86] In addition, the key toxicities associated with tamoxifen were not present (endometrial cancer, venous thromboembolic disease). Typical adverse events associated with AIs reflect the estrogen deprivation incurred in the presence of these agents: arthralgias, myalgias, and decreased bone density. Interestingly, few of these events were significantly elevated with anastrozole compared to placebo. The authors concluded that "anastrozole effectively reduces incidence of breast cancer in high-risk postmenopausal women."[93]

Prostate Cancer Prevention Trials

The Prostate Cancer Prevention Trial (PCPT) was a phase III RCT evaluating the efficacy of a 5-alpha-reductase inhibitor, finasteride, for prostate cancer prevention. Finasteride inhibits the conversion of testosterone to dihydrotestosterone, which is a key promoter of prostate cancer. The study randomized 18,882 men older than 55 years without evidence of disease, based on a prostate-specific antigen (PSA) level of 3.0 ng/mL or less and normal digital rectal exam (DRE). Participants enrolled in the study from October 1993 to May 1997, and received finasteride 5 mg/day or placebo for 7 years.[57] The study was stopped earlier than intended when an interim analysis revealed prostate cancer incidence was lowered by 25% in the finasteride group compared to the placebo group. However, early findings also indicated those men in the finasteride group who developed prostate cancer were found to have higher-grade tumors (Gleason score 7–10) than men developing prostate cancer in the placebo group. A 2007 reanalysis of the original study results suggested that the increase in high-grade tumors with finasteride was likely due to selective inhibition of low-grade cancers.[94] A more recent follow-up of long-term survival among PCPT participants indicated a 30% reduction in prostate cancers overall; a 17% increase in high-grade cancers with finasteride versus placebo among the cases; and no significant difference between treatment groups in overall survival or survival after prostate cancer diagnosis.[95]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was designed to evaluate whether two nutritional supplements, selenium and vitamin E, are effective in reducing the incidence of prostate cancer in a high-risk male population.[96] The rationale for selecting selenium and vitamin E was based on promising activity demonstrated in two earlier RCTs. The selection of selenium was based on secondary findings from the National Prevention of Cancer (NPC) trial, which showed that prostate cancer incidence was reduced by 63% among men receiving daily selenium supplementation.[58] Vitamin E was chosen based on secondary findings from the Alpha-Tocopherol, Beta-Carotene (ATBC) study, which indicated a 32% reduction in prostate cancer incidence and a 40% reduction in prostate cancer mortality in men taking α-tocopherol (vitamin E).[97] SELECT accrued 35,533 male subjects between 2001 and 2004 in more than 400 sites across the mainland United States, Canada, and Puerto Rico. Study eligibility criteria included being a male aged 55 years or older, absence of prostate cancer, serum PSA level of 4 ng/mL or less, and negative DRE. African American men, due to their increased risk of prostate cancer, were eligible to enter the trial at age 50. Participants were randomized in blinded fashion to one of four groups: (1) oral selenium (200 μg/day of l-selenomethionine) and matched vitamin E placebo; (2) vitamin E (400 IU/day of all rac-α-tocopheryl acetate) and matched selenium placebo; (3) selenium + vitamin E; or (4) two placebos for the two nutrients. The study design included a planned follow-up of at least 7 years and a maximum follow-up of 12 years.

In October 2008, SELECT was stopped when results indicated that selenium and vitamin E, taken alone or together, did not reduce the incidence of prostate cancer.[62] In addition, this initial analysis of the SELECT data showed two trends that were concerning, though not statistically significant: (1) slightly increased incidence of prostate cancer in men taking vitamin E only and (2) slightly increased incidence of diabetes in men taking selenium only. A follow-up analysis, which included 521 additional cases, indicated that supplementation with vitamin E was associated with a significant 17% increase in the risk of prostate cancer in this population of healthy men.[98]

A more recent analysis addressed the association of prostate cancer risk with baseline level of selenium, as assessed in terms of toenail selenium.[99] Supplementation with selenium, either alone or in combination with vitamin E, had no effect on men with low selenium status but increased the risk of high-grade prostate cancer in men with higher selenium status at baseline. In contrast, vitamin E supplementation alone showed no effect in men with higher

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selenium status but increased the risks of both any-grade and high-grade prostate cancer in men with lower selenium status at baseline.

Clinical Trials and Observational Studies: Aspirin and NSAIDs

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are prime examples of agents that are being tested for repurposing in cancer prevention.[64] They have been associated with reduced risk of cancer in epidemiologic and clinical studies since the 1980s. In particular, aspirin—the oldest NSAID and one of the most commonly used drugs in the United States[100]—has emerged as one of the most promising chemoprevention candidates. By virtue of its widespread use, with multiple indications in a range of adult populations, a large body of data is available for analysis of its unintended effects, both positive and negative.

While aspirin has shown efficacy for analgesia and antipyresis as well as ischemic stroke and myocardial infarction prevention (the latter two in selected populations), it is associated with significant risks as well. In a recent international consensus statement, Cuzick et al.[101] concluded that the cancer-related benefits of daily use of aspirin 75–325 mg for at least 5 years outweigh the risks in the general population, and that these benefits are even more likely with longer use. Importantly, the evidence showed that whereas the aspirin-associated adverse effects (as well as the beneficial cardiovascular effects) begin and end during the period of drug administration, the cancer prevention effects appear only after 3 years of treatment but seem to continue for a long period after the end of the treatment period. This long carry-over effect is seen with tamoxifen as well.

Aspirin has most consistently been shown to reduce mortality for gastrointestinal cancers, particularly colorectal and esophageal cancer, although beneficial effects have been seen in gastric, breast, prostate, and lung cancer as well. Even with the relatively low incidence of esophageal adenocarcinoma, after 5 years of follow-up, reductions in mortality of 58% in randomized trials and 44% in cohort studies were reported. Likewise, incidence reduction was seen in case-control and cohort studies, at 27% and 43%, respectively.[102–106]

Immunoprevention: Vaccines

One area of intense research at the present time involves exploring a variety of methods to harness an individual's own immune system to fight cancer. Greater success is evident in cancer prevention than cancer treatment with this approach. This is largely due to the progressive deterioration of the immune system during carcinogenic progression; the immune system becomes increasingly suppressed by a process known as "immunoediting." As multiple components of the immune system become suppressed and less able to fight cancer (or infection), therapies aimed at recruiting these immunologic elements become less effective. The efficacy of immunologic therapies, such as vaccines, is far greater in the prevention setting, where fully competent immune systems are capable of mounting robust antitumor responses, leading to eradication of abnormal cells and/or preventing disease onset and recurrence; essentially, immunoediting has not taken over the immune system in this situation. The preferential success of preventive vaccination is also attributable to a minimal or nonexistent tumor burden.

Three basic approaches are being used to recruit the endogenous immune response to prevent cancer:

- Vaccines to prevent infection by agents that cause cancer
- Vaccines that target antigens found selectively in cancer cells: "tumor-associated antigens" (TAAs) or "tumor-specific antigens"
- Nonspecific immunomodulators that recruit components of the innate immune system to exert their anticancer effect

Vaccines for Infectious Cancers

The most obvious successes in immunologic approaches to cancer prevention involve the development of vaccines that prevent cancer by inhibiting the onset of factors known to initiate carcinogenesis. Preventing infection with viruses that cause cancer offers a case in point. Certain viruses, as well as some bacteria and parasites, have been shown in epidemiologic studies to have an association, shown to be causal, with carcinogenesis at specific disease sites.[107,108] Human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human herpes virus 8/Kaposi sarcoma herpes virus (HHV8/KSHV), and adult T-cell leukemia/lymphoma virus-1 (HTLV-1) are prominent among the oncogenic viruses.

For example, chronic HBV infection causes between 50% and 90% of hepatocellular cancers (HCCs) in adults, with HCV accounting for most of the remaining cases.[109,110] In 2005, HPV, HBV, and HCV were the first viruses to be labeled as known human carcinogens by the U.S. Department of Health and Human Services (DHHS) in its *National Toxicology Report*.[111] These viruses and other infectious agents, such as *Helicobacter pylori*, are responsible for 10% to 20% of cancers worldwide.

Administration of prophylactic vaccines to protect against cancer-causing viruses is a relatively new medical approach in cancer prevention, and is appropriate if three conditions are met: (1) A microorganism is the known etiologic source of cancer, (2) vaccination can effectively prevent infection from the microorganism, and (3) prevention of infection by the microorganism can prevent cancer from developing.[111,112] Although the association between microorganisms and cancer development has been under investigation for close to half a century, only over the past several decades have vaccines slowly entered mainstream practice.

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The identification of HBV as a major cause of liver cancer/hepatocellular carcinoma instigated an effort to develop an HBV vaccine. The first prophylactic HBV vaccine, which is based on purified S particles from the virus, received FDA approval in 1982. It has proved 95% effective in preventing hepatitis B[113] and its use has led to an estimated 69% reduction in the incidence of HBV-specific HCC worldwide. The vaccine is recommended for all infants, older children and adolescents who were not previously vaccinated, and adults employed in healthcare settings (owing to their exposure to blood).[114] While effective vaccines against HCV or HIV (which predisposes infected individuals to certain cancers by virtue of its immunosuppressive effect) are not currently available, investigative efforts in these areas are ongoing. The next step will be to develop HBV and HCV therapeutic vaccines for cancer prevention in individuals who are already infected.

A similar trajectory has transpired in recent years for cervical cancer, which is induced through infection with specific strains of the human papillomavirus. According to the Centers for Disease Control and Prevention (CDC), HPV is the most common sexually transmitted disease in the United States, and is responsible for causing nearly all cases of cervical cancer.[115] Although only a small percentage of women with HPV develop cervical cancer, between 250,000 and 1 million American women are diagnosed with cervical dysplasia, a potential precursor to cervical cancer caused by the virus.[18] Certain HPV types may also be associated with some head and neck cancers (e.g., oropharyngeal and throat cancers).[116] HPV is also associated with anal cancer.

Two highly effective vaccines that target the L1 protein, a component of the outer shell of human papilloma virus, have been developed and licensed.[117,118] In the United States and the European Union, Gardisil (Merck), which targets HPV strains 6 and 11, which cause nearly 90% of genital warts, and the oncogenic strains 16 and 18, which are responsible for 70% of cervical cancers, was approved in 2006 for young females aged 9–26. In 2009, the FDA approved Cervarix (GlaxoSmithKline), which targets HPV strains 16 and 18, for females aged 10–25. The CDC's Advisory Committee on Immunization Practices (ACIP) officially recommends that females ages 11–12 receive the vaccine, and further indicates that females as young as age 9 and as old as age 26 are also candidates for immunization.[119] As of late 2007, approximately 25% of U.S. females ages 13–17 years had received at least one of the three HPV injections.

Although less than 25% of HPV-associated cancers occur in men overall, some subgroups are particularly susceptible to such cancers.[120] Among anal cancers, 90% are HPV related. In addition, recent data have shown a steady increase in HPV-positive oropharyngeal cancer in men.[121] Taken together, these observations suggest that HPV vaccination should be extended to prevent a broader range of HPV-associated cancers, beyond cervical cancer. Thus, current interest in the HPV vaccines now centers on expanding coverage to include boys.[120]

Additionally, efforts are underway to develop an HPV vaccine that can cure previously infected individuals, including those with existing premalignant lesions.[122] HPV vaccines seem to exhibit reduced efficacy in individuals with prior exposure to HPV, however.[120] Modeling analysis of their cost-effectiveness suggests vaccination to be a beneficial intervention in high-risk men for prevention of genital warts, oropharyngeal and anal cancer.[123]

Importantly, not all oncogenic strains of HPV are targeted by current prophylactic vaccines, and research to expand coverage is ongoing. A nonavalent vaccine that targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is now in advanced stages of development.[124] Nevertheless, a need still exists for Papanicolaou tests (Pap smears), as the remaining uncovered strains will continue to pose an oncogenic challenge to the cervix until even broader coverage is provided by multivalent vaccines. Even with broad coverage, the challenge of adherence to vaccination guidelines remains, pointing to a continuing need for Pap smear screening in specific populations of women.

H. pylori, a gram-negative, spiral, microaerophylic bacterium, infects more than 50% of the population worldwide. It has been associated with increased risk of gastric carcinomas and lymphomas.[125,126] Successful development of vaccines to prevent or treat *H. pylori* infection has proved elusive. Despite this, research is ongoing using a variety of antigens and adjuvants to elicit immune responses to this cancer-causing bacterium.[127]

Vaccines for Noninfectious Cancers

The selection of antigens as targets for vaccines for cancers not associated with exogenous infectious agents poses a special challenge. Such vaccines must be targeted to "tumor antigens," which are endogenous ("self") proteins that are aberrantly expressed.[128] Tumor-specific antigens are expressed only in cancer cells and germ cells. In contrast, TAAs occur normally in adult somatic cells but are modified in cancer cells. The mechanisms responsible for the transition of these normal cell regulatory proteins to aberrant ("abnormal self"), and therefore immunogenic, proteins in malignant cells are not fully understood. Some of the mechanisms underlying this transition include the acquisition of stable mutations (as is evident in melanoma antigen MAGE1); overexpression of the tumor-associated protein (such as ERBB2, also known as HER2 and neu), revealing additional epitopes that are not routinely exposed; and post-translational modification of a normal self-antigen, as is seen with abnormal glycosylation of MUC1 in colon cancer.[129]

Healthy individuals who do not have invasive cancer but who are at increased risk of developing cancer are the

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perfect candidates for cancer preventive vaccines, in large part because they still retain intact immune systems. In addition, individuals whose high-risk status is based on a history of precancerous lesions should benefit from vaccines more than those with invasive, especially widespread, cancers, because precancers tend to be small lesions and, therefore, are more likely to be controlled by an effective immune response. Both of these features support the notion that immunological approaches may be better suited for cancer prevention or early-stage treatment than for treatment of late-stage cancers.

Vaccination against MUC1 offers a concrete example of the efficacy of preventive vaccination in a mouse model of colitis-associated colon cancer (CACC). MUC1 is a normal protein expressed in normal epithelial cells lining glandular tissues, including the colon. However, it is abnormally expressed in inflammatory bowel disease (IBD), just as it is in colon cancers.[129] Vaccination of the mice against MUC1 not only delays IBD onset but also prevents progression to CACC, at least in part by eliciting MUC1-specific adaptive immunity, which eliminates abnormal MUC1-expressing cells in IBD-affected colons.

In a second example, in patients with breast cancer, cellular immunity (both CD4+ and CD8+ T cells) to three TAAs typically found in tumor tissue—ERBB2, carcinoembryonic antigen (CEA),[130] and melanoma-associated protein 3 (MAGE3)—was increased relative to controls.[130] A multi-antigen, multi-peptide vaccine targeting three TAAs was tested in a transgenic mouse model of breast cancer. These TAAs are proteins known to be expressed in preinvasive breast lesions: neu/HER2, insulin-like growth factor-1 receptor/IGF-1R, and IGF binding protein/IGFBP-2.[131] Immunization with all three antigens elicited a potent immune response in the form of CD4+ T cells and significantly reduced the number of mammary gland tumors that developed, emphasizing the potential of TAA-targeted vaccines for cancer prevention.

Antigen-specific cancer vaccines targeting such TAAs have been shown to elicit tumor-suppressive responses in the clinical setting as well.[132–134] Admittedly, the responses were incomplete, but they offer proof-of-principle for this approach to preventing invasive disease. A large number of clinical trials have been performed using different TAAs, and most have shown minimal toxicities and side effects that are common with any vaccinations.[132,134,135]

Nontargeted Immunological Preventive Interventions

In addition to vaccines and other interventions that target specific antigens, many agents elicit nonspecific immunologic responses, invoking the "innate" immune system. A number of these nontargeted immunomodulators have proved useful in preventing the initiation or progression of carcinogenesis, and some have already been approved by the FDA for use in the setting of cancer prevention.

Imiquimod (Aldara) represents one such success with a nontargeted intervention. Both this immunologic agent and a sister compound, resiquimod (R-848; Biovision, Milpitas, CA), activate the innate immune system through the toll-like receptors TLR-7 and TLR-8. Imiquimod applied topically was originally approved by the FDA to treat actinic keratosis, superficial basal cell carcinoma, and external genital warts. An 80% cure rate has been seen for lentigo maligna with imiquimod, and this agent has shown efficacy in vulvar intraepithelial neoplasia.[136] In a recent, small clinical trial, imiquimod showed benefit as an adjunct to surgery for high-risk, primary melanoma.[137] Like other TLR agonists, imiquimod has been shown to behave as an adjuvant and enhance antitumor activity when combined with a viral vector vaccine. An example of this application of imiquimod is its coadministration with an adeno-associated virus CEA vaccine.[138]

Carrageenans make up a family of linear sulfated polysaccharides that are derived from red algae and related to heparin sulfate. They possess nonspecific immunomodulatory properties, activating macrophages and inducing proinflammatory cytokines.[139] Carrageenan binds the innate immune systems' TLR-4, through which the agent confers its immunological effect. In vitro and animal studies have suggested that carrageenan may be a potent inhibitor of HPV infection.[140] In a clinical trial involving 1723 high-risk, sexually active women, Carraguard (FMC Biopolymer, Philadelphia, PA), a carrageenan-based lubricant, showed a reduction in HPV infection among women using the lubricant compared to those who did not.[141] Its ability to protect against vaginal transmission of HPV suggests a role for this nonspecific immunomodulator in prevention of HPV-associated cancers.

Immunostimulatory drugs have long been used for treatment of cancer and other diseases. Instillation of Bacillus Calmette-Guérin (BCG) into the bladder is an established treatment to prevent recurrence of superficial bladder cancer.[142] Among patients with high-grade T1 bladder cancer, nonspecific immunomodulation by BCG instillation following transurethral resection[143] showed a benefit on long-term follow-up; despite this, more than 3 years of follow-up indicated progression in 30% of patients. Ultimately, the goal is to predict which patients will develop recurrent disease and, in turn, improve the use of this approach. As an example, one study has shown that urinary interleukin-2 (IL-2) may be a promising predictive biomarker of BCG response.[144]

Several drugs have been developed that target distinct regulatory elements of the immune system that suppress the immune response to cancer. One such regulatory element is cytotoxic T-lymphocyte antigen 4 (CTLA4), which is expressed on the surface of T-helper cells and transmits inhibitory signals to T cells, to prevent the over-activation and prolongation of the immune response. Although desirable in normal tissue as part of the suppression of autoimmune activity, immunotherapy of cancer is impaired by

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inhibitory signals of this nature. Ipilimumab, a drug that inhibits CTLA4, has been approved by the FDA for treatment of metastatic or unresectable melanoma. Hence, while clinical studies have shown promise for this approach in advanced cancer, concern exists that such agents will produce unacceptable side effects, including autoimmune reactions in the prevention setting, which involves healthy individuals with intact, fully functional immune systems. Initial findings have indicated that targeting another T-cell inhibitory molecule, PD-1, might have benefits in combination with fewer side effects.[145] Nevertheless, further research is needed to examine the net balance between efficacy and toxicity.

Screening

Screening for early detection has been an important component of cancer prevention practice since the 1940s, when the Papanicolaou (Pap) test for cervical cancer was developed. The overall goal of cancer screening is to decrease cancer mortality—that is, deaths due to the specific cancer for which the screening test is devised. Screening for cancer is defined as searching for cancer or for conditions that may lead to cancer in individuals who have no symptoms. The assumption underlying the rationale for screening is that detecting cancer early (before it has become symptomatic) will enable it to be treated early and result in better outcomes, including better survival. An important distinction must be made between screening tests that look for cancer (in an effort to detect it early) in asymptomatic individuals versus diagnostic tests, which are administered to individuals who already exhibit signs and/or symptoms that are consistent with a possible cancer.

Screening for a given disease is recommended only under specific circumstances. Among the most important of these are (1) the disease/health condition represents an important health problem, with high rates of incidence and mortality; (2) the disease has a known natural history, with a high rate of prevalence in the preclinical (asymptomatic) or early symptomatic phase, sometimes called a "reservoir" of preclinical lesions; (3) an effective treatment is available should a cancer be detected; and (4) an appropriate test or examination is available that is acceptable to the population. Based on these criteria, not all malignancies are amenable to screening.[146] Ideally, an effective screening test has the following attributes:

- The test is sensitive—individuals with cancer have a positive test.
- The test is specific—individuals without cancer have a negative test.
- The test is associated with a high positive predictive value—individuals with a positive test have cancer.
- The test is associated with a high negative predictive value—individuals with a negative test do not have cancer.[147]

Screening tests should also be safe, inexpensive, minimally invasive, and easily accessible to all populations.[148]

Despite the potential benefit of cancer screening in terms of decreased mortality rates, a number of risks are associated with screening that are not always appreciated:[146,149]

- Complications associated with the screening procedure itself (i.e., bowel perforation associated with colonoscopy).
- False-positive test results that lead to unnecessary anxiety and invasive diagnostic procedures, which have their own complications.
- False-negative test results that can delay diagnosis and treatment of true disease at an early stage when cure may be more obtainable with treatment.
- Over-diagnosis—the diagnosis and treatment of disease that otherwise may have gone undetected and remained clinically insignificant for the remainder of an individual's life.[150]

Using the word "cancer" to describe a screen-detected lesion that will never progress meaningfully in a person's lifetime can also have negative implications in the psychological (perceiving oneself as a "patient"), medical (potential for unnecessary or over-treatment), and economic realms.[151]

Because these complexities are inherent in all screening tests, individuals should discuss the benefits and risks of cancer screening with their healthcare professional prior to screening.[152] Ideally, as with other medical prevention interventions, screening tests should be validated in phase III RCTs to determine efficacy compared to harms prior to implementation of the test in mass screening programs. Unfortunately, this sequence of "evidence for net benefit preceding uptake" in practice is frequently circumvented.[149] The intuitive appeal of screening for early detection of cancer is alluring to both the public and health professionals.[150]

Screening Modalities

Pap Smear for Cervical Cancer. The most widely used screening programs have addressed early detection of cancers of the cervix and breast. Since its introduction in the 1940s, the Pap smear has become a standard screening practice. In 2008, approximately 80% of women between 18 and 64 years of age reported having had a Pap smear in the previous 3 years.[153] This percentage dropped to 50% after age 65, which may be reasonable. A recently published population-based case-control study showed that women who had adequate negative screening at ages 50–64 years had one-sixth of the risk of cervical cancer at ages 65–83 years compared with women who had not been screened.[154] These data suggest that discontinuation of screening after age 60 may be reasonable in some women.

Prior to the advent of screening, cervical cancer was the leading cause of cancer death among women. Since that time, mortality from cervical cancer has declined sharply in

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the United States and other developed countries, although in underdeveloped countries it remains a significant cause of cancer deaths.

The identification of a causal relationship between HPV and cervical cancer provides one more opportunity for early detection through screening. In this case, the screen is not directly for cancer, but rather for a virus that must be present for the cancer to develop. Incorporating HPV viral testing into the screening algorithm allows for less frequent cytologic (Pap smear) testing. Thus, the United States Preventive Services Task Force (USPSTF) recommends cervical cancer screening in women ages 21–65 years with cytology (Pap smear) every 3 years or, for women ages 30–65 years who want to lengthen the screening interval, screening with a combination of Pap smear and HPV testing every 5 years.[155] In fact, in 2012 the guidelines from three key organizations—the USPSTF, the American College of Obstetricians and Gynecologists (ACOG), and the American Cancer Society (ACS)—became consistent. The USPSTF, for example, recommends (1) no screening with Pap smears in women younger than 21 years regardless of sexual activity; (2) a screening interval (Pap smear) of 3 years for women ages 21–65; and (3) for women ages 30–65 who want to lengthen the screening interval, screening with Pap cytology together with HPV testing every 5 years.[155]

Mammography and Breast Magnetic Resonance Imaging. Mammographic screening for breast cancer has been a mainstay of early detection for many years, resulting in a 28% to 65% reduction in the rate of death from breast cancer, depending on the model used.[156] In women at average risk, the ACS recommends clinical breast exam (CBE) at least every 3 years for women in their 20s and 30s, and annually for women older than age 40. The ACS recommends that annual mammographic screening begin at age 40.[157] In 2009, the USPSTF updated its evidence-based guidelines to recommend against routine screening mammography for women ages 40–49.[158] For women ages 50–74, the USPSTF's recommendations were reduced to biennial mammographic screening. The evidence for CBE was deemed to be insufficient to merit a recommendation at the time.[158]

The USPSTF's cutting back on screening indications reignited an ongoing controversy on the topic of mammographic screening. The scientific evidence supporting this reduction in screening frequency goes against the intuitive sense that "more is better."[149] The USPSTF bases its recommendations on evidence from clinical trials, always weighing the potential harms against the potential benefits. The downside of intensive screening includes false-positive mammograms, which are common and lead to undesirable sequelae such as invasive procedures, which carry their own risk of adverse effects, as well as increased anxiety and its impact on subsequent health-related behaviors.[159] The same types of adverse outcomes are associated with over-diagnoses, another category of screening observations that includes lesions that look like cancer but are destined not to progress in any meaningful way during the person's lifetime.[146]

The heated response to the 2009 USPSTF recommendations was amplified further with publication of the 25-year follow-up of the Canadian National Breast Screening Study, an RCT initiated in 1980 that randomized 89,835 women ages 40–59 to mammography or no mammography. This long-term follow-up analysis confirmed earlier findings that the cumulative mortality due to breast cancer was similar in the two arms.[160] Yet, the clash between scientific evidence from this trial and intuition[149] again rekindled impassioned expressions of conflicting views on the value of mammographic screening. Clarity can be achieved only if women are apprised of the benefits (reduction in breast cancer deaths) as well as the harms (false-positive results with resulting biopsies and over-diagnoses with overtreatment) of screening.[161]

Despite conflicting recommendations, mammography remains the most widely used cancer screening test available. Efforts to develop biomarkers that might identify women with a higher risk of breast cancer are under way; such biomarkers would help guide who should have more intensive screening. Molecular approaches are also likely to expand in the years ahead as more is learned about the genetics of breast cancer. Molecular markers may also be useful in identifying those women who are likely to benefit from specific medical interventions.

Digital mammography and magnetic resonance imaging (MRI) represent technological advances that can enhance the ability to detect cancers at an early stage, when treatment opportunities may be more effective and allow for increasing survival. Digital mammography goes beyond traditional mammography in that it is capable of capturing, storing, and then manipulating electronic images for enhanced evaluation. In the Digital Mammographic Imaging Screening Trial (DMIST), conducted by the American College of Radiology Imaging Network (ACRIN), digital mammography was compared to traditional film mammography.[162] Although study results in the general population were similar for both technologies, digital mammography showed greater efficacy in detecting and staging of breast cancers at earlier stages for women in several subgroups: (1) women younger than age 50, (2) premenopausal and perimenopausal women, and (3) women with radiographically dense breasts.[162]

MRI has been tested in clinical trials, in particular for women with a familial or genetic predisposition to breast cancer.[163] Because of its high sensitivity (which is accompanied by low specificity), MRI has been useful for screening in women who are known carriers of genetic mutations that predispose them to cancer, including women with *BRCA1*

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and *BRCA2* gene mutations.[164,165] The ACS recommends an annual MRI in conjunction with mammography for breast cancer screening in this high-risk population.

Prostate-Specific Antigen for Prostate Cancer. Since its introduction as a screening test in 1987, PSA has been widely used for that purpose in healthy men older than age 50, increasing detection of latent disease from a large reservoir of preclinical prostate lesions.[166] Use of this test rapidly became widespread despite the absence of scientific evidence that PSA screening actually results in a decrease in prostate cancer mortality. Population data document increases in incidence coinciding with adoption of PSA testing. In the same time frame, however, mortality rates remained stable or showed at most only a mild decrease—a scenario that is highly suggestive of over-diagnosis of prostate cancer.[167] Two large phase III RCTs were implemented to investigate which benefits and harms are associated with PSA screening of healthy men (discussed later).

Colonoscopy and Fecal Tests for Colorectal Cancer. Although screening has been shown to be effective for decreasing cancer incidence and mortality rates for colorectal cancers, it has not been nearly as well accepted as screening tests for breast and cervical cancers.[168] While clinicians have decades of experience with fecal occult blood test (FOBT) screening for the presence of blood in the stool, several newer tests are also available. The fecal immunochemical test (FIT) is similar to standard FOBT, but does not require certain food or drug restrictions that might interfere with screening results prior to testing. FIT provides superior sensitivity with similar specificity to traditional tests.[169] Stool DNA tests have also been developed to identify DNA mutations in stool samples. In addition, a recent trial comparing various colorectal screening methods reported that high-resolution computed tomography colonography (CTC) is comparable to traditional colonoscopy, with sensitivities approximately equal in identifying polyps larger than 5 mm.[170] The NCI is conducting clinical trials to determine the most efficient and cost-effective manner to screen people for colon cancer; clinical trials are also seeking to determine the best population-wide strategies for improving screening participation.[171]

A large body of research has suggested a variety of reasons for the low uptake of screening for colorectal cancer as well as strategies for overcoming these barriers. A number of studies have reported that lack of awareness about colorectal cancers as well as screening options and recommendations are major factors in low screening participation.[172–174] Among interventions that were tested to improve screening rates, those that involved in-person individual or group educational sessions were most successful.[175] Nurses are uniquely positioned to increase patient knowledge in this area during one-on-one interactions with patients and their family members.

Screening Trials

Prostate, Lung, Colorectal, and Ovarian (PLCO). The PLCO trial is an example of a large NCI-sponsored cancer screening trial. The PLCO was designed to determine whether early detection through screening effectively lowers mortality rates for cancers of the prostate, lung, colon and rectum, and ovary, which collectively account for approximately 45% of all cancer deaths in the United States annually.[18,176]

The PLCO screening tests comprise the following: (1) chest x-ray for lung cancer and sigmoidoscopy for colon cancer for all study participants; (2) cancer antigen 125 (CA-125) and transvaginal ultrasound for ovarian cancer; and (3) PSA and DRE for prostate cancer. The PLCO accrued study subjects between 1993 and 2001, randomizing 155,000 males and females to one of two groups: (1) an intervention group receiving serial screening exams over 6 years, with a 7-year follow-up period, or (2) a control group receiving routine care from their healthcare providers, with a 13-year follow-up period. A key feature of the PLCO study design is a biorepository containing specimens obtained from study participants at baseline and throughout the study. The specimens are available to researchers throughout the country via a competitive process overseen by a PLCO review committee, to identify, develop, and validate biomarkers of risk and early detection.[177]

The prostate cancer screening component was the first disease site to meet its primary screening endpoint, prostate cancer mortality. At 13 years of extended follow-up, data continue to show no evidence of a mortality benefit for annual screening compared with the usual care (i.e., control) arm.[178]

In the lung cancer screening component of PLCO, 77,455 subjects were randomized to annual screening with postero-anterior view chest radiographs, while 77,456 control group participants were randomized to usual care. The primary endpoint was lung cancer mortality rates; secondary outcomes included lung cancer incidence rates and all-cause mortality. Results over a 13-year follow-up period showed no difference in lung cancer mortality between the two groups.[179]

Colorectal cancer incidence and mortality were evaluated in the colorectal screening component of PLCO. Again, 77,445 participants were randomized to initial screening with flexible sigmoidoscopy and repeat screening at 3 or 5 years, while 77,455 were randomized to the usual care (control) group. With more than 10 years of follow-up, results continue to show significant decreases in colorectal cancer incidence and mortality rates for individuals in the flexible sigmoidoscopy group as compared to the usual care group.[180]

In the ovarian component of PLCO, 78,216 women were randomized to receive annual screening with CA-125 and transvaginal ultrasound annually for 4 years. Individuals in the control group were not offered screening but were

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advised to seek usual care. Participants were followed for a maximum of 13 years. The primary endpoint was ovarian cancer mortality; secondary outcomes included ovarian cancer incidence and complications associated with screening examinations and diagnostic procedures. Results showed that screening with CA-125 and transvaginal ultrasound did not reduce mortality from ovarian cancer.[181]

European Study of Screening for Prostate Cancer (ERSPC). The ERSPC, another large, randomized, controlled prostate cancer screening trial, enrolled 162,387 men in the core 55- to 69-year-old group (a subpopulation of the 182,000 men aged 40–74 in a larger randomized group). The participants were randomized to screening every 4 years at most of the trial's European centers versus usual care.

At an average follow-up time of 8.8 years, a 71% higher incidence of prostate cancer was observed with screening versus usual care.[182] At 11 years' median follow-up, the risk ratio was 0.79 (95% confidence interval [CI], 0.68–0.91; $p = 0.0001$) for prostate cancer-related death in the screening group versus the control group, representing an absolute reduction of 0.10 death/1000 men.[183] The inconsistency of the ERSPC's findings of a significant 20% (9 years) and 21% (11 years) risk reduction in the rate of prostate cancer–associated death with PSA-based screening versus the PLCO trial's findings are likely due to the considerable differences in the trials' study designs.

Based in part on the clear evidence of over-diagnosis and resulting overtreatment, along with uncertain evidence of benefits, including inconsistency between the two major prostate cancer screening trials, the USPSTF issued a recommendation against routine prostate cancer screening in 2012.[184] In sum, the current evidence supports a discussion between an average-risk man between ages 55 and 69 years and his clinician about the pros and cons of PSA screening. Only men expressing a distinct preference for screening should be offered PSA testing.

National Lung Screening Trial (NLST). The NLST is another major NCI-sponsored screening study, conducted in collaboration with PLCO investigators and the American College of Radiology Imaging Network (ACRIN).[185] Although lung cancer is the leading cause of cancer mortality for men and women in the United States, an effective validated screening test was not available at the time of study initiation. NLST evaluated two screening modalities—low-dose computed tomography (LDCT), also known as helical CT, and chest x-ray—in 53,000 smokers and former smokers over 8 years at 30 sites nationwide. LDCT is a scanning technology in which a CT scanner rotates around a subject who is positioned on an x-ray table that passes through the center of the scanner. Helical CT allows low-resolution images of the entire thorax to be captured in a single breath-hold, reducing the chance of artifact. Computer-generated images are assembled into a three-dimensional model of the thorax using one-tenth the radiation dose of a diagnostic CT scan.

Earlier, results from several observational studies had indicated that LDCT was able to detect tiny abnormalities in lung tissue, generally too small to be identified on chest x-ray.[186,187] However, it was unclear to the research community whether detection of such miniscule abnormalities translated into an advantage for reducing mortality. Consequently, the NLST was designed as a definitive RCT to evaluate the true mortality effects of low-dose CT and chest x-ray. Results from this study, which were released in November 2010, showed that participants who received LDCT scans had a 15% to 20% lower risk of dying from lung cancer than participants who received standard chest x-rays. This is equivalent to approximately three fewer deaths per 1000 people screened in the CT group compared to the chest x-ray group over a period of about 7 years of observation (17.6/1000 versus 20.7/1000, respectively).[188,189]

In 2013, the USPSTF recommended lung cancer screening with LDCT for patients at high risk for developing lung cancer. The USPSTF issued a B recommendation, indicating a likelihood of "moderate to substantial" net benefit.[190] This triggered coverage for screening with LDCT by private health insurers under the provisions of the Patient Protection and Affordable Care Act (PPACA). In November 2014, the Centers for Medicare & Medicaid Services (CMS) proposed a decision in favor of annual LDCT lung cancer screening for high-risk individuals covered by Medicare, albeit with some restrictions, according to a preliminary decision from the agency.[191] The proposed decision calls for LDCT to be reimbursed for beneficiaries who fit the criteria of the pivotal NLST: individuals ages 55–74; having at least a 30 pack-year history of smoking; and being a current smoker or one who quit in the prior 15 years.

CANCER PREVENTION, THE PUBLIC, AND PUBLIC POLICY

PATIENT PROTECTION AND AFFORDABLE CARE ACT

The PPACA was enacted by Congress in 2010, marking the greatest change in U.S. public health policy in 50 years. The law represents a major opportunity for prevention of disease and enhancement of public health, as it establishes the National Prevention Strategy, which provides new funding for prevention and public programs and promotes the use of preventive clinical services.[192,193]

The PPACA has several major aims. The primary aim is to achieve near-universal health insurance coverage and to do so through shared responsibility among government, individuals, and employers. A second aim is to improve the fairness, quality, and affordability of health insurance

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coverage. A third aim is to improve healthcare value, quality, and efficiency while reducing wasteful spending and making the healthcare system more accountable to a diverse patient population. A fourth aim is to strengthen primary healthcare access while bringing about longer-term changes in the availability of primary and preventive health care. A fifth aim is to make strategic investments in the public's health, through both an expansion of clinical preventive care and community investments.[194] Several key health prevention areas are targeted by the fifth aim, including tobacco control and cessation, the effects of obesity, and prevention-focused clinical trials.

TOBACCO

At the individual level, the PPACA requires that all health plans must cover tobacco cessation counseling without cost sharing. At the national level, the Public Health and Prevention Fund supports smoking cessation support lines, health department infrastructure, and many other critical preventive services.[195] In addition, the U.S. Department of Health and Human Services is implementing new research and surveillance activities to address knowledge gaps related to tobacco prevention and control. Prevention and treatment interventions for high-risk populations are being planned based on current research activities.[192]

OBESITY

The PPACA identifies obesity as a substantial health threat to the nation and addresses specific challenges to be met by the act. For example, directives for new health plans established under the PPACA include coverage, with no cost sharing, for obesity screening and counseling for children and adults.[192] The PPACA further promotes attainment and maintenance of healthy weight by appropriating funds through 2014 for demonstration projects intended to develop model programs for reducing childhood obesity. Additionally, chain restaurants will be required to label their menus to disclose specific nutritional information on food products and in vending machines. Importantly, the PPACA states, "The health of the individual is almost inseparable from the health of the larger community. And the health of each community and territory determines the overall health status of the Nation."[196]

CLINICAL TRIALS

Section 10103(c) of the PPACA added a new provision to the federal Public Health Service Act, which imposes requirements on group health plans and health insurance issuers offering individual or group health insurance products to provide coverage of routine patient costs associated with approved clinical trials. The provision, included in section 2709 of the Public Health Service Act, specifies:

> Prohibition on denials of coverage or on discrimination. With respect to plan years beginning on or after January 1, 2014, if a group health plan or health insurance issuer offering group or individual coverage provides coverage to a qualified individual, then the plan or issuer is prohibited, under federal law, from doing any of the following: a) denying the individual participation in an approved clinical trial, b) denying or limiting, or imposing additional conditions on the coverage of routine patient costs for items or services furnished in connection with participation in the approved clinical trial or, c) discriminating against the individual on the basis of the individual's participation in the approved clinical trial.[193,194,196–198]

Clinical trial participation is essential if researchers are to obtain evidence-based data regarding cancer prevention and treatment. The policy regulating payment for clinical trials will likely have a positive impact on accrual, especially for under-represented populations, which include adolescents, older adults (65 years and older), individuals of low SES, individuals living in rural areas, African Americans, Latinos/Hispanics, Asian Americans and Pacific Islanders, and American Indians/Alaska Natives.[199,200] In addition, a new policy aimed at increasing insurance reimbursement for physicians willing to participate in community clinical trials will likely improve accrual among populations covered by Medicare and Medicaid. The net result is expected to be an acceleration of accrual, thereby decreasing the duration of what are now lengthy clinical trials. In addition, study results would be more generalizable because of the inclusion of these subpopulations.

CANCER PREVENTION CHALLENGES

As the science of prevention evolves, we are presented with a variety of challenges and opportunities. One of the primary challenges is to gain better understanding of the molecular events underlying carcinogenesis and to translate that information into clinical practice. Currently, the drug development process is painstakingly slow, but the recent introduction of phase 0 trials should prove effective in shortening the time an agent spends in the clinical trials system. Another major issue in cancer prevention is the presence of misleading and confusing information. At times, conflicting accounts of the benefits and harms associated with nutritional or dietary supplements may be reported in the press simultaneously. Conflicting or partial reports contribute to confusion among information-seeking recipients and healthcare providers alike. Furthermore, data from observational studies have not always been consistent with findings from clinical trials. For example, numerous observational studies have reported a strong inverse association

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between increased intake of fruits and vegetables (which are rich in beta-carotene) and lung cancer incidence. Based on these data, a large RCT, the beta-carotene and retinol efficacy trial (CARET),[53] was designed to evaluate and validate these supplements as means of lung cancer prevention. In a disappointing outcome, increased lung cancer incidence and mortality rates were found for smokers and former smokers receiving beta-carotene.

The clinical trials process presents many interesting challenges for researchers. Definitive chemoprevention trials are costly and lengthy, and require large numbers of participants, but have a great potential for public benefit. Issues related to the difficulty of conducting such large phase III trials include less than optimal numbers of individuals willing to participate in clinical trials and difficulties in reaching underserved populations. The differences between chemotherapy treatment trials and chemoprevention trials underscore some of the unique challenges in these areas. Chemopreventive agents must have extremely low toxicity profiles, much lower than is acceptable in treatment trials for late-stage cancers. Prevention trials utilize cancer incidence or mortality endpoints, which are more difficult to attain than the disease response endpoints that serve as a metric of success or failure in treatment trials. For this reason, surrogate endpoints, mainly biomarkers, are being developed that may serve as substitutes, but they remain in the exploratory phase. Surrogate endpoints for adverse events also would be useful. Finally, high-risk study subjects are more difficult to identify and enroll in prevention trials than are individuals with cancer in treatment trials.

Risks and perceptions associated with cancer screening present obstacles to successful mass screening for some diseases. For instance, despite evidence that screening reduces mortality rates for colorectal cancers, only 50% of individuals in the age group recommended for screening by the USPSTF undergo screening.[201] Lack of insurance and access are some of the obstacles. In addition, a lack of educational programs and materials presented at low reading comprehension levels and in foreign languages contributes to poor screening rates, by leading to a misunderstanding or lack of knowledge about available options.[201]

Screening tests also have associated risks. No screening test has 100% sensitivity and specificity, and false-positive and false-negative readings may occur. On the one hand, false-positive test results cause unwarranted anxiety in tested individuals while they pursue diagnostic workups. On the other hand, individuals with false-negative screening results may experience false reassurance, thereby losing valuable diagnostic and treatment time, and having lowered opportunities for survival.

Finally, downstream harmful effects associated with screening tests affect not only individuals, but also the healthcare community and society. For instance, LDCT is capable of detecting tiny lung abnormalities, an unknown number of which may never develop into cancers. However, once identified, the nature of a lesion must be pursued. No one can estimate the number of avoidable invasive (including surgical) procedures that are performed in pursuit of nonsignificant lesions identified on LDCT, the associated morbidity and mortality rates, or the associated personal and public financial impact. Moreover, even though the NLST showed a mortality benefit associated with use of LDCT for screening certain high-risk cohorts, it should not be used in the general population. As directed by the USPSTF, eligibility is to be determined by the eligibility criteria in the NLST.

NURSING IMPLICATIONS

Various classification systems have been used to categorize prevention activities into different levels. To be consistent with current nursing literature, this chapter defines the levels of cancer prevention as primary, second, and tertiary.

Primary prevention refers to the decrease of cancer incidence due to behavioral or medical intervention. Such prevention strategies can be population based or focused on specific high-risk subgroups. Adopting health-protective lifestyle behaviors that include healthy diet, physical activity, tobacco abstinence, and avoidance of excessive direct sunlight are examples of primary prevention activities that target the general population. By comparison, chemoprevention—that is, administration of a chemical compound or nutritional supplement—targets high-risk individuals only, and is used to prevent the development of a specific malignancy.

Secondary prevention refers to reduction in cancer mortality by means of early detection through screening. The benefits of screening include potential diagnosis of cancer at an early, preclinical stage, while an individual is still asymptomatic and treatment may be more successful.

Tertiary cancer prevention is a term that applies to prevention and reduction of morbidity and mortality of clinically evident cancer through diagnosis and treatment. As such, it is discussed elsewhere in this text.

As the landscape of cancer prevention evolves, nurses must strive to keep pace with the advances in technologies, medical interventions, and risk factor modifications. In the future, they will still be expected to perform traditional cancer prevention functions such as identifying unhealthy behaviors and their consequences (i.e., tobacco use, obesity) and providing education and counseling related to healthier lifestyle choices and cancer screening. With more than 40 million current smokers in the United States, it is vital that nurses educate themselves and other healthcare providers about tobacco dependence and evidence-based interventions to assist with smoking cessation. Nursing interventions, such as tobacco counseling, have been shown to increase smoking cessation and improve outcomes. A

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variety of initiatives supported by government and nongovernment organizations have been developed to provide educational programs and guidelines for increasing awareness of the dangers associated with smoking and to offer recommendations to lower smoking prevalence rates.

In addition to conventional responsibilities, more complex nursing roles have evolved in areas related to cancer prevention. These increased prevention-related responsibilities will become more important as the demands on a physician's time result in less physician-to-patient discussions regarding healthy lifestyle modifications, screening recommendations, and chemoprevention and chemoprevention trial options for high-risk individuals. Indeed, cancer risk assessment has become a large part of the prevention nurse's role. Risk assessments include an evaluation for increased cancer risk due to behavioral, physiological, environmental, and family history and genetic factors. Nurses should be actively involved in identifying these high-risk individuals for inclusion in chemoprevention clinical trials and for appropriate use of approved chemopreventive interventions in the general clinical setting. Nurses perform a variety of roles in the conduct of prevention trials. Some are involved with data collection and management and conducting data quality assurance to ensure accuracy and timeliness of the information. An important component of clinical trials nursing is identifying, reporting, and observing for trends in adverse events, especially serious adverse events.

Another area of opportunity is genetics. Given the shortage of trained genetic counselors, nurses have often assumed this role in cancer settings. Nurse geneticists provide education and guidance related to the implications of genetic contributions to disease.

Nurses have also begun to pursue graduate and doctoral degrees in greater numbers in the areas of nursing informatics, genetics, and clinical trials to support prevention science. Doctorally prepared nurses have begun teaching in subspecialty areas related to cancer prevention. In this manner, nurses are gaining expertise in clinical trials, nursing informatics, genetic risk assessment, and other areas—a trend that will establish nurses as key players in the field of cancer prevention in the future.

Organizations such the Oncology Nursing Society, International Society of Nurses in Genetics, and National Society of Genetic Counselors provide a wealth of supportive and educational resources for nurses interested in broadening their understanding of prevention. These organizations, and others, provide professional guidelines and standards for practice, as well as online educational courses, publications, continuing education programs, and other materials related to cancer prevention and genetics-related information. The NCI's Division of Cancer Prevention also provides online information regarding cancer prevention and behavioral risks, chemoprevention, screening, and descriptions of completed and ongoing clinical prevention trials. In the long term, nurses can effect major changes in cancer prevention health policy by functioning as change agents and advocates for tobacco control policies, healthy school lunch programs, physical fitness curricula, diet and nutritional awareness, immunization agendas, and clean air programs in their workplaces and communities. Nurses are practicing in a new era where making appreciable changes in the lives of many individuals through cancer prevention is a reality.

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