Cancer Prevention: The Roles of Diet and Chemoprevention

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Considerable evidence links dietary factors with cancer risk, but ongoing investigation is needed.

Background: Reduction of cancer risk by either preventing carcinogenesis or stopping carcinogenesis in its early stages is a logical approach for reducing the cancer burden, both for high-risk individuals and for the general population. The areas of dietary modification and chemoprevention show considerable promise as effective approaches for cancer prevention and are a focus of research efforts.

Results: Diet and cancer studies show that, generally, vegetables and fruits, dietary fiber, and certain nutrients seem to be protective against cancer, whereas fat, excessive calories, and alcohol seem to increase cancer risk. Chemoprevention research is closely linked to diet and cancer research and represents a logical research progression.

Conclusions: Dietary epidemiologic studies have helped to identify many naturally occurring chemopreventive agents. Currently, randomized clinical prevention trials sponsored by the NCI include dietary interventions (eg, low-fat and/or high-fiber vegetables and fruits) targeting breast and colorectal cancer, chemoprevention trials using micronutrients (eg, vitamin E, calcium, vitamin D) aimed at lung and colorectal cancer, and chemoprevention trials testing the effectiveness of pharmaceutical agents (eg, tamoxifen, finasteride, aspirin) for breast, prostate, and colorectal cancer.

Introduction

In 1937, when the National Cancer Institute (NCI) was established, the cancer cell was largely a mystery, and scientific knowledge was mostly descriptive. Since then, particularly since the passage of the National Cancer Act in 1971 and the declaration of the “war on cancer,” research on carcinogenesis has led to the realization that cancer is not a single disease. Cancer is, in fact, a biomedically complex group of diseases resulting partly from changes in genes that control cell growth and behavior and partly from interactions between these genetic changes and the cellular stresses from specific environmental and behavioral factors, including lifestyle choices such as diet.

Advances in molecular biology and their applications to cancer have resulted in the development of sensitive and specific diagnostic techniques as well as improvements in therapies for cancer. Mortality rates for most cancers common in the United States are stable or declining, with the exception of increases in lung cancer mortality. However, cancer incidence rates rose between 1975 to 1979 and 1987 to 1991 by 12.4% in women and 18.6% in men, in large part due to increasing rates for prostate cancer in men and for breast cancer in women (both accounted for primarily by improved detection) and for lung cancer in women, a result of cigarette smoking.

An approach to reducing cancer risk that either prevents carcinogenesis or stops carcinogenesis in its early stages is a logical and perhaps the best strategy to reduce the overall cancer burden. The time worn adage, “an ounce of prevention is worth a pound of cure,” still holds true, as evidenced by the significant drop in mortality from coronary heart disease since 1973, which resulted in large part from recognizing precursors to coronary heart disease and adopting preventive measures to reduce risk.

Two major complementary programs at the NCI give high priority to cancer prevention. The diet and nutrition program conducts research in prevention related epidemiology, nutritional and molecular regulation, and dietary intervention trials to identify and evaluate cancer preventive dietary patterns. The chemoprevention program identifies and assesses specific chemical substances, many naturally occurring in foods, with the potential to prevent cancer initiation and to either slow or reverse the progression of premalignant lesions to invasive cancer.

Diet and Cancer

A large body of epidemiologic evidence, together with data from animal and in vitro studies, strongly supports relationships between dietary constituents and the risk of specific cancers. Generally, vegetables and fruits, dietary fiber, and certain micronutrients appear to be protective against cancer, whereas fat, excessive calories, and alcohol seem to increase cancer risk. However, the fact that not all data are consistent across studies is likely the result of several contributing factors. Foods are complex mixtures of nutrients and nonnutritive substances that are difficult to measure accurately, and the effects of individual constituents as well as the possible interactions among these constituents are difficult to unravel. Differences among individuals, including inherited genetic susceptibility, also could contribute to inconsistent epidemiologic associations between dietary factors and specific cancers. For example, a polymorphism in N-acetyltransferase - an enzyme that catalyzes the formation of mutagenic products from heterocyclic aromatic amines, which are substances formed in cooked meats and fish-- classifies individuals into slow and fast acetylators. Compared with slow acetylators, fast acetylators have a reported 80% greater risk for colorectal cancer; also, risk increases with levels of meat.
consumption in fast acetylators but not in slow acetylators.8 As another illustration, a recent study demonstrated that dietary risk factors for colorectal cancer are associated with p53 subtypes. Specifically, cruciferous vegetables may be protective for colorectal cancer development through a p53-dependent pathway, whereas beef consumption may increase risk for colorectal tumorigenesis through a p53-independent pathway, thus contributing to the difficulty of interpreting epidemiologic data.9 Even though inconsistencies may be observed and the interpretation of data on diet and cancer associations may not always be straightforward, available data have provided valuable leads for generating hypotheses for further research.

**Dietary Fat**

Epidemiologic data suggest a direct relationship between total fat intake or consumption of animal fat and increased cancer risk at several sites, including the postmenopausal breast, the colon/rectum, and the prostate.5,6,10-12 Migrant studies show that changes toward a high-fat, low-fiber "Western" diet result in a rise in breast cancer incidence. Data for Asian-American women born in the West indicate a breast cancer risk 1.6 times higher than that for Asian-American women born in the East.13 Case-control and cohort studies, however, have not found a clearly significant association between fat intake and breast cancer incidence. A meta-analysis of 23 studies by Boyd and colleagues14 reported a summary relative risk (RR) of 1.21 for case-control studies and 1.01 for cohort studies, similar to a recent meta-analysis of cohort studies15 that found a summary RR of 1.05. Several factors could contribute to the lack of conclusive epidemiologic evidence between total fat intake and breast cancer risk, including importance of diet before adulthood, differences in methodologies, insufficient variation in fat intake within a population, effects of correlated variables, and variations in genetic susceptibility and breast tumor heterogeneity within the populations studied.

International correlation studies show strong associations between colorectal cancer incidence and intake of red meat or animal fats.5,6,11 Also, data from case-control and cohort studies, including studies that use adenomatous polyps as markers of risk, generally support the associations with red meat, but data for fat intake is less consistent.16-19 For example, data from a cohort of more than 47,000 American male health professionals found no significant risk association with any type of fat but showed a significantly elevated risk of colon cancer associated with red meat intake (RR = 1.71). This association was not confounded by other dietary factors, physical activity, body mass, alcohol intake, cigarette smoking, or aspirin use.16

Cross-cultural and migrant studies support the suggestion that a "Western" diet is associated with increased disease risk for prostate cancer as well as for breast and colorectal cancers.5,6 A review of epidemiologic studies found that numerous case-control and cohort studies indicate that a consistent relationship between prostate cancer and consumption of either fat or high-fat foods, especially red meat.20 A recent study21 of the relationship of prostate cancer with diet in blacks, whites, and Asians in the United States and Canada reported a significant direct association with saturated fat, with highest risks for Asian-Americans. However, estimates suggest differences in saturated fat intake accounted for only approximately 10% of black/white differences and approximately 15% of Asian-American/white differences in prostate cancer incidence, thus supporting a hypothesized etiologic role for other environmental factors or genetically determined variations.21

The type of fat appears to be important in cancer development. For example, data from international correlation and case control studies link animal fat and red meat to colon cancer risk but do not support an association between colon cancer and vegetable fat.5,6,11,17 For prostate cancer, some data suggest that alinoenic acid appears to increase disease risk (RR=3.43), whereas saturated fat (RR=0.95), monounsaturated fat (RR= 1.58), and linoleic acid (RR=0.64) show no significant associations.22 The relationship between breast cancer and type of fat is unclear. Based on international food disappearance data, consumption of both saturated fat and omega-6 polyunsaturated fat has been correlated with increased breast cancer risk.11 In a recent study,23 however, saturated fat showed no association (RR=0.95), whereas total polyunsaturated fatty acids (RR=0.70) and oleic acid (RR=0.81), a monounsaturated fatty acid, showed inverse associations with breast cancer risk. Also, consumption of olive oil, in which oleic acid is a major component, appears to reduce breast cancer risk (RR=0.87).24 In international correlation studies, highly unsaturated omega-3 fatty acids -- found primarily in fish oils -- are not associated with increased breast cancer risk and have been hypothesized to be protective.11,25

**Vegetables, Fruits, and Whole Grains**

Epidemiologic data provide strong evidence that high intakes of vegetables, fruits, and whole grains are associated with reduced cancer risk. Comprehensive reviews of case control and prospective cohort studies found that the relationship between high vegetable and fruit intake and reduced cancer risk appears to be strongest for cancers of the alimentary and respiratory tracts (cancers of the colon, lung, esophagus, and oral cavity) and weakest for hormone-related cancers (cancers of the breast, ovary, cervix, endometrium, and prostate).26-28 Many studies showing a protective role for vegetables and fruits indicate approximately twice the risk of cancer incidence for lowest vegetable and fruit intakes compared with highest intakes.26-28 Reduced cancer risk has been linked primarily to consumption of raw vegetables and fresh fruits (citrus, carrots, green leafy vegetables, and cruciferous vegetables), soy products, and whole grain wheat products.26-29 The beneficial effect of vegetables, fruits, and whole grains may be due to either individual or combined effects of their constituents, including fiber, micronutrients, and phytochemicals. The latter are naturally occurring and mostly nonnutritive compounds found in plants. Although specific constituents have been the focus of numerous studies, the relative cancer-protective contributions of the nutrients and nonnutrients that are "packaged" in fruits, vegetables, and whole grains are difficult to separate.

**Dietary Fiber**

Dietary fiber, which is generally defined as a group of endogenous compounds in plant foods that are resistant to human digestive enzymes, may play a beneficial, although still not fully defined, role in reducing cancer risk. Epidemiologic studies generally endorse the cancer-protective properties of dietary fiber and fiber-rich foods, and some indicate that fiber may modulate the risk-enhancing effects of dietary fat.5,30 For example, colon cancer risk was lower in Finland, where the average fiber intake was twice that in Denmark and New York, even though all three populations had a high fat intake (34% to 37%).31,32 The type of fiber may be important to cancer risk reduction; wheat bran appears to inhibit colon tumor development in animals more effectively than other fiber sources.30 Current animal studies are focusing on the differences in possible protective mechanisms of various fiber types at different subsites within the colon.31,34

Although some epidemiologic evidence suggests an inverse relationship between intakes of fiber and fiber-rich foods and breast cancer risk, the influence of fiber per se on breast cancer development, relative to the contributions of other constituents in fiber-rich foods, is not yet clear.35,36 - The risk of breast cancer, as well as other hormone-dependent cancers, may be influenced by dietary fiber through alteration of hormone production, metabolism, or actions at the cellular level.36 Dietary fiber may influence estrogens -- primarily associated with breast cancer etiology -- through alteration of the microbial population and enzymes in the intestinal tract, reducing the deconjugation of estrogens and, thus, the amount available for reabsorption. Also, phytoestrogens, which appear to compete with estrogens for receptor-binding sites, thus potentially reducing breast cancer risk, are produced in the intestine from fiber-related precursors.37

**Micronutrients**
Epidemiologic studies have demonstrated cancer-protective relationships for foods high in antioxidants such as vitamin C, beta-carotene, vitamin E, and selenium, as well as the micronutrients vitamin A, calcium, and folate. Data from these studies have provided consistent support for the protective effects of foods containing vitamin C for cancers of the stomach, esophagus, and oral cavity and moderate protective effects for cancers of the cervix, rectum, breast, and lung. Recent clinical trial data support a possible protective effect for vitamin E for colorectal and prostate cancer, and most epidemiologic studies link increased dietary calcium with a decreased risk of colon cancer.

Interest in beta-carotene as a potential anticancer agent escalated in the 1980s. Results from both case-control and cohort studies show a consistent association for foods high in beta-carotene and reduced risk for lung and stomach cancers. Several possible mechanisms, including conversion to vitamin A and antioxidant activity, support the biologic plausibility of beta-carotene as protective against some cancers.

**Phytochemicals**

Vegetables, fruits, and whole grains contain a wide variety of phytochemicals (eg, terpenes, organosulfides, isothiocyanates, indoles, dithiolthiones, polyphenols, flavonones, tannins, protease inhibitors, and non[vitamin A]-active carotenoids) that have the potential to modulate cancer development. For example, common vegetables and fruits contain approximately 50 carotenoids, which are compounds that, as a class, exhibit strong antioxidant activity. Lutein (abundant in yellow/orange vegetables and fruits) and lycopene, the most abundant carotenoid (found almost exclusively in tomatoes and tomato-based foods) exhibit exceptionally strong antioxidant activity. Recently, a large prospective epidemiologic study reported that increased intakes of lycopene and tomato-based foods may be associated with reduced cancer risk.

The specific mechanisms of action of most phytochemicals in cancer prevention are not yet clear but appear to be varied. For example, brassinin, found in cabbage, may block carcinogen activation by inducing phase II enzymes involved in xenobiotic detoxification; curcumin, a component of turmeric, may inhibit colon tumorigenesis by modulating arachidonic acid metabolism. Considering the large number and variety of dietary phytochemicals, their interactive effects on cancer risk may be extremely difficult, if not impossible, to separate definitively.

**Alcohol**

Epidemiologic data indicate that associations between alcohol consumption and cancer vary by site and type of alcoholic beverage. Alcohol intake is reported to be directly associated with cancers of the oral cavity, pharynx, esophagus, and larynx, where alcohol acts synergistically with smoking to increase risk. Breast, colorectal, liver, and pancreatic cancers also have been linked to alcohol intake. A meta-analysis of studies linking alcohol consumption and breast cancer incidence reports an estimated 25% increase in risk for daily alcohol intake equivalent to two drinks, as well as a dose-response relationship. Analysis of data from the Health Professionals Follow-up Study showed that men who drank more than two drinks daily, containing approximately 30g of alcohol, had twice the risk of developing colon cancer, especially of the distal colon, as men who drank less than one quarter of a drink daily. Inadequate intake of folate and methionine increased alcohol-associated risk for cancer of the distal colon approximately sevenfold, even after adjustment for age, history of polyps/endoscopy, smoking, level of physical activity, body mass index, intakes of red meat and total energy, and multivitamin use.

**Chemoprevention**

Chemoprevention is a promising and relatively new approach to cancer prevention that has a precedence in cardiology, in which cholesterol-lowering, antihypertensive, and antplatelet agents are administered to prevent coronary heart disease in high-risk individuals. The concept of using chemopreventive agents to reduce cancer risk is firmly based on epidemiologic and experimental evidence from the last two decades that indicates specific compounds may influence carcinogenesis at various sites, including the oral cavity, esophagus, stomach, colon/rectum, lung, breast, and prostate. Individuals at high risk for specific cancers, as determined by detection of genetic mutations, currently have limited options to reduce that risk. For such individuals, a chemopreventive strategy could potentially either prevent further DNA damage that might enhance carcinogenesis or suppress the appearance of the cancer phenotype.

The NCI's chemoprevention program, initiated in the early 1980s, has developed into a major effort in which more than 400 potential chemopreventive agents are being studied, including more than 25 compounds in approximately 60 ongoing clinical trials. Chemoprevention uses a stepwise, systematic research strategy that includes (1) identification of potential new agents that have either efficacy in preventing carcinogenesis in animal models or a high probability, based on epidemiologic studies, of preventing human cancer, (2) preclinical drug development, and (3) phases I, II, and III clinical intervention trials.

**Research Leads**

Chemoprevention research is necessarily linked to diet and cancer research and represents a logical research progression. Dietary epidemiologic studies have provided initial leads for the identification of numerous naturally occurring candidate chemopreventive agents, and laboratory studies have identified many potential agents that suppress carcinogenesis in animal models. Promising chemopreventive agents being investigated include micronutrients (eg, vitamins A, C, and E, beta-carotene, molybdenum, calcium), phytochemicals (eg, indoles, polyphenols, isothiocyanates, monoterpenes, organosulfides), and synthetics (eg, vitamin A derivatives, proxicam, tamoxifen, 2-difluoromethylthione [DFMO], and olitpraz).

Broadly defined on the basis of their mechanisms of action, chemopreventive agents can be grouped into two general classes: blocking agents and suppressing agents. Blocking agents (eg, flavonoids, olitpraz, indoles, isothiocyanates) prevent carcinogenic compounds from reaching or reacting with critical target sites by preventing the metabolic activation of carcinogens or tumor promoters by enhancing detoxification systems and by trapping reactive carcinogens. Suppressing agents (eg, vitamin D and related compounds, nonsteroidal anti-inflammatory drugs [NSAIDs], vitamin A and retinoids, DFMO, monoterpenes, calcium) prevent the evolution of the neoplastic process in cells that would otherwise become malignant. Mechanisms of action for suppressing agents are not well understood. Some produce differentiation, some counteract the consequences of genotoxic events such as oncogene activation, some inhibit cell proliferation, and some have undefined mechanisms. Certain chemopreventive agents may exhibit several different mechanisms of action simultaneously.

**Preclinical and Early-Phase Clinical Testing**

Preclinical development for chemopreventive agents includes assessment of compound efficacy using in vitro cell-screening systems and site-specific, whole-animal in vivo assays. Based on the results, compounds are then prioritized for extended efficacy, preclinical toxicity, and clinical testing. Agents found to have high efficacy and low toxicity at this phase of development are assigned high priority for clinical evaluation. Phase I clinical trials, which generally use a limited number of healthy human subjects, are designed to determine the dose-related safety and toxicity of the proposed chemopreventive agent. The dose and schedule of administration are based on achieving plasma levels in humans that are likely to be safe and to show effectiveness based on the preclinical toxicity and efficacy data from animal and in vitro
Phase II clinical trials evaluate agent efficacy in a larger group of subjects at high risk for specific cancers. They also provide data that characterize dose, safety, and toxicity in the selected population. Two important objectives of phase II trials include (1) identifying biochemical, genetic, cellular, or tissue biomarkers of cancer that can be used to estimate the potential for neoplastic progression and (2) determining whether the chemopreventive agent being tested can affect the modulation of that biomarker. The NCI currently is sponsoring approximately 30 phase II trials that are targeting cancers of 10 different organ systems: colon, prostate, lung, breast, bladder, cervix, oral cavity, esophagus, skin, and liver. Agents found to have high efficacy and low toxicity in phase II clinical trials are investigated further in large-scale phase III intervention trials conducted with a large number of subjects over an extended period. Selected examples of phase II and phase III chemoprevention trials currently sponsored by the NCI are presented in the Table.

### Biomarkers

The validation of biomarkers that can detect early, specific changes correlated significantly to carcinogenesis reversal or progression is crucial for progress in cancer prevention. Used as predictors of cancer, these biomarkers can help to identify high-risk individuals who could serve as target populations for intervention trials. As surrogate endpoints, biomarkers have the potential for assessing the efficacy of preventive interventions with cost effectiveness and a relative speed that are not possible when cancer incidence is used as the endpoint. In addition to improving trial efficiency, biomarkers are essential to applied prevention research because of their unique potential to provide insights into mechanisms of action as well as sound rationales for the design of large-scale trials.58,60

Despite the identification and investigation of numerous potential biomarkers, no intermediate endpoint has yet been validated as an accurate predictor of future cancer incidence. Examples include genetic markers (eg, nuclear aberrations [such as micronuclei], gene amplification, and mutation), cellular markers (eg, differentiation markers and measures of proliferation, such as thymidine labeling index), histologic markers (eg, premalignant lesions, such as leukoplakia and colonic polyps), and biochemical and pharmacologic markers (eg, ornithine decarboxylase activity). Several factors are considered when evaluating the potential of an intermediate biomarker to serve as an endpoint in clinical prevention studies. The biomarker must be expressed differently in normal and high-risk tissue, with clear evidence of progression from normal tissue to biomarker to cancer. The intermediate biomarker should be on the causal pathway for carcinogenesis or closely associated with the pathway and, ideally, should appear early in carcinogenesis, thus providing a greater chance for achieving successful preventive intervention with a consequent reduction in cancer risk. Acceptable intermediate biomarkers must be highly sensitive, specific, and reproducible, and they must be modulatable by the preventive intervention being evaluated. Further, the validation of biomarkers as endpoints in prevention research requires correlation of their modulation to a decreased rate of a related cancer.58,60

NCI-sponsored phase II clinical trials are currently testing chemopreventive agents using a variety of dysplasia-based histologic biomarkers, including prostatic intraepithelial neoplasia, cervical intraepithelial neoplasia, ductal carcinoma in situ, dysplastic oral leukoplakia, colorectal adenomas, bronchial dysplastic metaplasia, and actinic keratosis.

### Large-Scale Intervention Trials

Randomized, large-scale phase III clinical trials are generally considered the best means available to test whether dietary or chemopreventive interventions reduce cancer risk. Usually involving thousands of subjects, these trials can take 10 years or longer to complete and include studies in high-risk populations as well as in the general population. Although the primary objective of phase III trials is to determine the cancer-preventive effectiveness of the intervention, they also provide opportunities to attempt to validate potential biomarkers as surrogate endpoints for cancer.

### Polyp Prevention Trial

The Polyp Prevention Trial is a multicenter, randomized, controlled dietary intervention trial that is examining the effect of a low-fat (20% of calories from fat), high-fiber
Because such polyps are precursors of most colorectal cancers, an intervention that reduces polyp occurrence has a strong probability of reducing cancer incidence. Men and women aged 35 years and older are eligible to participate in the Polyp Prevention Trial if they have had one or more adenomatous polyps removed within six months of randomization and no history of colorectal cancer, inflammatory bowel disease, or large bowel resection. Between June 1991 and January 1994, 1,037 individuals were randomized to the intervention and 1,042 to the control group. Participants will receive extensive dietary and behavioral counseling on how to meet their dietary goals. Controls are expected to continue their customary dietary intake. This trial, which provides 90% power to detect a reduction of 24% in the annual adenoma recurrence rate, is expected to be completed in early 1998.

**Women's Health Initiative**

The Women's Health Initiative, which began in fall 1993, is a 10-year, multidisciplinary trial that includes both dietary and chemopreventive interventions. This trial is examining the effects of (1) a low-fat eating pattern (20% of calories from fat) that is high in vegetables, fruits, and fiber, (2) hormone replacement therapy, and (3) calcium and vitamin D supplementation on the prevention of cancer, cardiovascular disease, and osteoporosis in approximately 63,000 postmenopausal women of all ages and socioeconomic strata. In addition to the randomized clinical trial, the Women's Health Initiative includes prospective surveillance of another 100,000 women for etiologic factors and predictors of future illnesses. Also, community-based intervention studies will seek effective ways to promote behaviors aimed at preventing cancer, cardiovascular disease, and osteoporosis.

**Linxian Trials**

The Linxian Trials, conducted by the NCI in collaboration with the Chinese Institute of the Chinese Academy of Medical Sciences, consisted of two randomized, double-blind chemoprevention trials to determine whether daily ingestion of vitamin/mineral supplements would reduce incidence and mortality rates for esophageal cancer in a high-risk population in Linxian, China, where approximately 20% of all deaths result from esophageal cancer. The General Population Trial began in 1986 and randomized more than 30,000 individuals. Participants received one of four combinations of supplements each day for five years at doses equivalent to one to two times the US Recommended Daily Allowances (RDAs). Combinations included retinol and zinc; riboflavin and niacin; vitamin C and molybdenum; and beta-carotene, vitamin E, and selenium. The second study, the Dysplasia Trial, enrolled 3,318 individuals with evidence of severe esophageal dysplasia. Over a six-year period, they were randomized to receive either a placebo or a daily supplement of 14 vitamins and 12 minerals at two to three times the US RDAs.

Results of the General Population Study indicated a significant benefit for those receiving the beta-carotene/vitamin E/selenium combination -- a 13% reduction in cancer mortality, due largely to a 21% drop in stomach cancer mortality. Also, this group experienced a 9% reduction in deaths from all causes, a 10% decrease in deaths from strokes, and a 4% decrease in deaths from esophageal cancer. Although the effects of the beta-carotene/vitamin E/selenium combination began to appear within one to two years after the intervention began and continued throughout the study, the three other combinations did not affect cancer risk. A nonsignificant 16% reduction in mortality from esophageal cancer was reported for the Dysplasia Trial.

Analysis of esophageal dysplasia data showed that supplementation had a significant beneficial effect. Individuals receiving supplements were 1.2 times as likely to have no dysplasia after 30 and 72 months of intervention compared with individuals receiving the placebo. Postintervention follow-up is continuing. The results of these trials are encouraging but may not be directly applicable to Western cultures, which tend to be well nourished and not deficient in multiple micronutrients compared with the Linxian community.

**Women's Health Study**

The Women's Health Study is a chemoprevention trial that was designed to evaluate the risks and benefits of low-dose aspirin and the antioxidants beta-carotene and vitamin E in the primary prevention of cardiovascular disease and cancer in healthy postmenopausal women in the United States. Begun in 1992, this study will enroll approximately 40,000 female nurses who are 45 years of age and older and who have no history of either disease. Participants are randomized to treatment or placebo groups for four years following a three-month prerandomization run-in phase. In response to the lack of benefit for beta-carotene seen in the Beta-Carotene and Retinol Efficacy Trial (CARET), the Physicians' Health Study (PHS), and the Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC), the Women's Health Study has now removed beta-carotene supplementation from its intervention. The study will continue to evaluate aspirin and vitamin E.

**Breast Cancer Prevention Trial**

The Breast Cancer Prevention Trial is a 10-year, multicenter chemoprevention study testing the ability of tamoxifen, a synthetic compound that has antiestrogenic activity, to prevent the development of breast cancer in healthy women at increased risk for developing the disease as determined by age, number of first-degree relatives with breast cancer, age at first live birth, number of benign breast biopsies, age at menarche, and presence of atypical hyperplasia. This study, which began in 1992, focuses on women at high risk for breast cancer, because the potential benefits of tamoxifen must be weighed against an increased risk for endometrial cancer and other possible side effects. Based on previous clinical experience with tamoxifen, it has been estimated that tamoxifen may reduce the incidence rate of breast cancer in high-risk women by at least 30%. Approximately 16,000 women over 35 years of age are receiving either oral tamoxifen (20 mg/d) or placebo for an initial period of five years. Although the major endpoint of this trial is the incidence of breast cancer in trial participants, there will be additional analyses of cardiovascular effects and alterations in bone/mineral metabolism.

**Prostate Cancer Prevention Trial**

The Prostate Cancer Prevention Trial is a multicenter chemoprevention trial designed to investigate the ability of finasteride to prevent the development of early-stage prostate cancer in men considered to be at increased risk for the disease based on age (more than 90% of prostate cancers are diagnosed in men ages 55 or older). Because the development of early-stage prostate cancer appears to be strongly influenced by hormones, particularly dihydrotestosterone (DHT), inhibiting the synthesis of this hormone by administration of finasteride also may inhibit development of prostate cancer. In this trial, which began in 1993, approximately 18,000 healthy men 55 years of age and older with prostate-specific antigen levels less than 3 ng/mL and with no evidence of prostate cancer on physical examination receive 5 mg of finasteride or placebo orally each day for seven years, after which time they will undergo prostate biopsies.

**Completed Beta-Carotene Trials**

Large-scale, randomized, controlled chemoprevention trials using beta-carotene include PHS, CARET, and ATBC. PHS, which began in 1982, is a general population trial in 22,000 US physicians that evaluated the effects of aspirin and beta-carotene supplementation on the primary prevention of cardiovascular disease and cancer. The aspirin component of PHS ended in 1987 because a benefit of aspirin on risk of first heart attack (44% reduction) was found. The treatment period for beta-carotene continued until December 1995; data showed no significant evidence of benefit or harm from beta-carotene for either cardiovascular disease or cancer.
ATBC and CARET were both conducted in populations at high risk for lung cancer. ATBC, conducted in Finland, investigated the efficacy of vitamin E (alpha-tocopherol) alone, beta-carotene alone, or a combination of the two compounds in preventing lung cancer among more than 29,000 male cigarette smokers who were 50 to 69 years of age, with an average treatment/follow-up of six years. Unexpectedly, ATBC showed a 16% higher incidence of lung cancer in the beta-carotene group, with the greatest risk observed in the heaviest smokers and in persons with a higher alcohol intake (independent of smoking). The beta-carotene group also had an 8% higher risk of total deaths, primarily due to more deaths from lung cancer and ischemic heart disease. However, 34% fewer cases of prostate cancer and 16% fewer cases of colorectal cancer were diagnosed among men who received vitamin E. CARET tested the efficacy of a combination of beta-carotene and retinol (as retinyl palmitate) in men and women who were former heavy smokers and in men with extensive occupational asbestos exposure. This trial was halted in January 1996 after four years of treatment, when data showed a 28% higher incidence of lung cancer in participants receiving the beta-carotene/retinyl palmitate combination.

Further, the trend for increased lung cancer incidence among those receiving beta-carotene was similar to that in ATBC -- the major factor in the decision to stop CARET. Data from both ATBC and CARET support the hypothesis that, in current smokers, supplemental beta-carotene may have a promotional effect on lung cancer subsequent to interaction with high-intensity cigarette smoke, because beta-carotene products that have pro-oxidant activity are formed. Overall, the results of PHS, ATBC, and CARET suggest that the cancer-protective effect observed for vegetables and fruits may be a result of actions and interactions of a number of naturally occurring constituents in these foods, and that isolating the effects of specific constituents may prove to be difficult.

Future Research Directions

The scope of future cancer prevention strategies could be broadened considerably by combining chemoprevention approaches using either a single agent or a combination of agents with modifications in eating behavior. Such strategies may reduce cancer incidence and mortality through early intervention for individuals who are at increased risk for specific cancers. Developing effective methods for identifying individuals at high risk will become increasingly important. The medical community can play an important role in identifying such individuals who may benefit from preventive interventions specifically tailored for their particular risk profiles based on genetic factors, lifestyles, environmental exposures, history of precursor lesions, or a combination of these factors. Recognizing genetic polymorphisms that affect the susceptibility of individuals to carcinogens, such as polymorphisms in the GST genes that encode glutathione-S-transferases (enzymes that are important in the detoxification of reactive electrophiles), will be an important step in developing logical and effective preventive approaches. Further, identifying subtypes of disease based on etiologic mechanisms also may help to formulate preventive approaches for individuals with specific susceptibilities. Examination of breast tumors, for example, has demonstrated that not all breast tumors are alike (tumors may exhibit different acquired genetic alterations), thus providing support for considering breast cancer as a heterogeneous disease that consequently may respond to a variety of preventive approaches.

Because carcinogenesis may span 20 years or more for certain cancers, researchers have potential opportunities to suppress the disease in its early, premalignant stages before clinical, invasive disease develops. The biomedical community, when developing strategies for significantly reducing cancer incidence and mortality, both overall and for specific cancers, must recognize and emphasize the potential of a preventive approach to cancer. Advances in diagnostic and therapeutic techniques have eased the burden of cancer. However, a concentrated focus on cancer prevention by all members of the biomedical community, including cancer researchers and medical practitioners, is needed to generate the greatest possible progress against this complex group of diseases.

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