CHAPTER

18

The Challenge of Nutrition in Cancer Prevention

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OVERVIEW OF THE NUTRITION–CANCER RELATIONSHIP

Compelling evidence continues to accumulate to strengthen the link between diet and cancer. Information comes from a wide range of research initiatives, including population-based studies, ecological studies, human metabolic studies, methodology development, investigations of the basic mechanisms of action of dietary constituents, and clinical trials of dietary modification and the chemopreventive potential of individual nutrients or dietary components. In addition, applicable knowledge of genetic, environmental, and molecular influences on carcinogenesis and the interaction of diet or dietary factors with these aspects are providing an interface for cancer prevention researchers to better assess cancer risk and intervene to reduce risk. The relationship between food and cancer and other chronic diseases, such as cardiovascular disease and diabetes, is tremendously complex. Although much progress has been made in understanding this complexity, it seems apparent that the majority of information remains to be discovered and many challenges exist. Possibly the most important lesson for nutrition research in the past decade has been recognizing the need for a new paradigm for discovering the role of nutrition and diet in disease prevention (Greenwald, 2001). This new approach will, by necessity, be more interdisciplinary and will incorporate advances in molecular biology, genetics, metabolic studies, and various other disciplines with clinical trials. By encompassing and integrating lifestyle and medical approaches, cancer prevention researchers will broaden the scope of research activities to develop compelling strategies to improve the public health. Understanding individual variability through enhanced use of emerging technologies and identification of risk profiles to target those who could benefit from lifestyle or medical interventions will fill the need for better research translation.

The new paradigm in nutritional oncology is developing in an environment of change in many fields of science. Advances in our understanding of the changes in the genetic and epigenetic environments after exposure to foods is driving the search for molecular targets and mechanisms that can be altered by dietary modifications, either alone or combined with other lifestyle choices. Along with new approaches to nutritional oncology, new terms have been developed to describe interactions among foods, genes, proteins, and cells (see Box 1). The interrelationships between bioactive food components (BFCs) and cellular processes, as currently understood, are depicted in Figure 1.

Nutritional oncology encompasses prevention of cancer in healthy individuals, prevention of recurring cancer in cancer survivors, and the impact of nutrition among patients undergoing treatment for cancer. Each of these areas is the focus of ongoing research as the role of nutrition in the cancer spectrum of prevention, screening and detection, diagnosis, treatment, and palliative care is determined and strategies developed. There are differences in the approach to nutritional intervention at each step of the spectrum, and health professionals should be aware of differences in recommending dietary or other lifestyle changes, especially before, during, and after cancer treatment (American Cancer Society, 2001; Shattner, 2003; Lada et al., 2004).

Systematic Approaches to Cancer Prevention

The overall research approach for cancer prevention begins with a systematic assessment of what people are

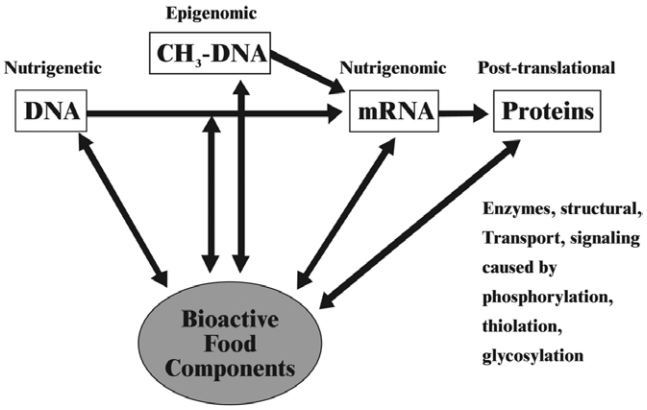

FIGURE 1 The interrelationship of factors that can influence the overall response to food components.

BOX 1 Nutritional Oncology Terminology

Bioactive Food Components
Compounds within foods that have a direct or indirect action on genetic or epigenetic structures and/or processes
Genomics
The study of genes and their functions
Nutrigenomics
The prospective analysis of differences among nutrients regarding the regulation of gene expression
Nutrigenetics
The genetic profile that influences absorption, metabolism, and site of action of the response of genes to bioactive food components
Epigenomics
The study of heritable changes in gene function that cannot be explained by changes in DNA sequence.
Proteomics
The study of protein shape, function, and patterns of expression
Metabolomics
The study of low-molecular-weight fractions of cells, tissues, and body fluids

eating, how nutrients and nonnutrient dietary constituents interact within the body, and other aspects of lifestyle—for example, weight gain, obesity, body mass index (BMI), and physical activity—that are affected by nutrition. One systematic approach, and the approach that is used as the template for this chapter, is the three-D (3-D) approach of *d*iscovery, *d*evelopment, and *d*elivery (von Eschenbach, 2003). The focus of the 3-D approach is on creating a research environment to integrate disparate research communities in an effort to enhance the search for clues to the diet–cancer link and to speed dissemination of research results to the clinician and the public.

- *Discovery* is the process that generates new knowledge about fundamental aspects of cancer-related processes at the genetic, molecular, cellular, organ, person, and population levels.
- *Development* is the process of creating and evaluating tools and interventions to reduce the cancer burden, including the prevention, detection, diagnosis, and treatment of cancer and its sequelae.
- *Delivery* is the process of disseminating, facilitating and promoting evidence-based prevention, detection, diagnosis, and treatment practices and policies to reduce the burden of cancer in all segments of the population. The focus of these efforts is on populations who bear the greatest burden of disease.

The 3-D approach has been developed as a seamless integrated template for initiating and conducting investigations for cancer prevention, not as a sequential approach most common to past research initiatives. Discovery, development, and delivery will be designed to proceed concurrently, with results from each initiative causing adjustments in each of the other initiatives or creation of new research paths. Investigations include both lifestyle and medical approaches, which have provided important clues to the role of nutrition in cancer risk.

Lifestyle Approaches

Nutrition and diet contribute ~35% to cancer risk, approximately the same risk contribution as tobacco smoking (Doll and Peto, 1981). An analysis of worldwide cancer incidence and mortality rates suggests that 3–4 million cancer deaths per year are attributable to dietary factors, with a stronger association among cancers that are not hormonally mediated (stomach and colorectal), compared with those that are (breast and prostate) (Young and LeLeu, 2002) (Table 1). Lifestyle approaches to cancer prevention may begin with changing dietary patterns that may

TABLE 1 Selected Cancers Related to Dietary Factors

Cancer	Estimated percent attributed to dietary factors
Breast	33–50%
Prostate	10–20%
Stomach	66–75%
Colorectal	66–75%
All cancers	30–40%

Source: Young and Le Leu (2002).

be addressed by the complete diet that impacts overall health and cancer, such as obesity. For example, although the U.S. population has decreased the amount of fat in the diet in the past 2 decades, portion sizes (particularly in restaurants), the number of daily calories consumed, the average weight of Americans (especially among adolescents), and the percentage of Americans who are obese have increased. The trend for the increasing prevalence of overweight and obesity is of special concern because of studies that show the negative impact of obesity on cancer risk. In the past decade, the prevalence of overweight (BMI 25.0–29.9) and obesity (BMI ≥30.0) among adults in the United States has increased from 56% to 64% (Flegal et al., 2002). The association between overweight and obesity and a significant risk of cardiovascular mortality has been known for some time; however, the magnitude of the significance for cancer mortality has not been quantified until recently (Calle et al., 1999). A prospective cohort study of more than one million adults in the United States assessed cardiovascular disease mortality and BMI and found a significantly increased risk of death among men (relative risk [RR] = 2.9) and women (RR = 2.37) (Calle et al., 1999). In a subsequent study of cancer mortality in the same cohort, the effect of overweight and obesity was found to contribute to 20% of cancer deaths in women and 14% in men (Calle et al., 2003). For specific cancer sites, there was a linear trend of increasing mortality from lower BMI to higher BMI for cancers of the stomach and prostate in men, and cancers of the breast, uterus, cervix, and ovary in women (Calle et al., 2003). According to this analysis, >90,000 cancer deaths in the United States each year could potentially be prevented if men and women maintained normal weight. Development of effective interventions to reduce the prevalence of overweight and obesity is essential. Research in experimental carcinogenesis models indicates that a regimen of caloric restriction (usually 20–40% relative to *ad libitum* controls), which reduces obesity, may be one of the best broad-based interventions to reduce cancer risk (Hursting et al., 2003), although few consistent data exist in humans. Caloric restriction has a beneficial impact on mechanisms regulated by insulin-like growth factor (IGF)-1, including cell proliferation, apoptosis, and cell cycle regulation. To illustrate, caloric restriction increases the rate of apoptosis by reducing the DNA synthesis, which is necessary to increase the number and volume of preneoplastic lesions (Hursting et al., 2003). Achieving a greater understanding of the relationship between obesity and increased cancer risk will require a concerted effort using an interdisciplinary approach of basic and clinical research.

As the U.S. population becomes heavier and less active, the challenge for modulating the impact of diet on chronic disease risk should become a national priority. Current trends begun in the past decade for "super-sizing" restaurant portions should be viewed as an impediment to a healthy populace. A study of marketplace portion sizes compared actual served portions with recommended federal portion standards and found most marketplace portions are two to eightfold larger than portions used in federal guidelines (Young and Nestle, 2003). A study of trends in portion sizes from national surveys from 1977 to 1996 found that food portion sizes increased both inside and outside the home for all categories except pizza (Nielsen and Popkin, 2003). In addition, energy intake and portion size of salty snacks increased by 93 kcal (60%), soft drinks by 49 kcal (52%), hamburgers by 97 kcal (23%), French fries by 68 kcal (16%), and Mexican food by 133 kcal (27%). A research center study of self-served portions versus larger served portions (double an age-appropriate portion) among children suggests that the larger served portion leads to an increase in entree size by 25% and total energy intakes by 15% (Orlet et al., 2003). A comparison of National Health and Nutrition Examination Survey (NHANES) III (1988–94) data and earlier studies from the 1970s on energy intake among children and adolescents (2–19 years of age) suggests that there has been little increase in energy intake (Troiano et al., 2001). The same study, however, did show that mean percentage of energy from total and saturated fat decreased but remained above recommendations, with overall means of 33.5% of energy from fat and 12.2% of energy from saturated fat. Because overweight and obesity in this age-group has increased over the past decades, some have suggested that decreasing levels of physical activity may account for this finding.

Regular physical activity is one of the most important modifiable risk factors for cancer after dietary choices and smoking. A review of evidence for an association between physical activity and cancer found convincing epidemiological evidence that regular physical exercise, comparing highest to lowest levels, reduces the risk of colon cancer by 40–50% and breast cancer by 30–40% (Friedenreich and Orenstein, 2002). For other cancer sites, this review reported that the association was probable for prostate cancer and possible for cancers of the endometrium and lung. Although the underlying mechanisms for the associations have not been established, possible mechanisms have been proposed. For example, mechanisms that may contribute to a beneficial effect of physical activity on colon cancer include changes in gastrointestinal transit time, altered immune function and prostaglandin levels, and changes in insulin levels, IGFs, bile acid secretion, serum cholesterol, and gastrointestinal and pancreatic hormone profiles (Quadrilatero and Hoffman-Goetz, 2003). Possible mechanisms for a physical activity–breast cancer relationship include decreased levels of exposure to estrogen, increases in the production of sex hormone–binding globulin, and reductions in circulating concentrations of insulin and related growth factors (Friedenreich and Orenstein, 2002). Based on accumulating evidence of the health benefits of physical

activity for cancer and cardiovascular disease, the American Cancer Society (2002) and other national organizations have adopted the recommendation that adults should engage in at least moderate activity for ≥30 minutes on 5 or more days of the week. Children and adolescents should engage in ≥60 minutes/day of moderate-to-vigorous physical activity at least 5 days per week.

Medical Approaches

Medical approaches to cancer prevention focus on designing and conducting preclinical and clinical studies to better understand the biological basis of the carcinogenic process and how to influence cancer risk. Chemoprevention (a pharmacological approach to intervention that aims to prevent, arrest, or reverse either the initiation phase of carcinogenesis or the progression of premalignant cells) is an important part of the medical approach developed for cancer prevention and intervention. Laboratory and epidemiological studies have provided the scientific rationale for investigating potential chemopreventive agents (Greenwald et al., 1990). For example, epidemiological studies support an inverse relationship between the intake of vegetables and fruits and cancer risk, and clinical studies have identified possible phytochemical components of these foods (as well as interactions among the components) that might contribute to their ability to reduce cancer risk (Chemoprevention Working Group, 1999; Negri et al., 1991). To illustrate, among the hundreds of phytochemicals and micronutrients with potential chemopreventive effects identified from animal and *in vitro* studies, diallyl sulfide, a phytochemical found in *Allium* vegetables such as garlic and onion, has been associated with a reduced risk of prostate (Hsing et al., 2002) and colorectal and stomach cancers (Fleischauer et al., 2000). A review by Milner (2001a) found garlic protects against carcinogenesis by blocking *N*-nitroso compound formation, suppressing bioactivation of several carcinogens, induces apoptosis, alters the cell cycle, and alters several phase I and II enzymes associated with cancer initiation and progression. Understanding the mechanisms of action of dietary constituents such as garlic with confidence for translating this knowledge into prevention strategies remains a significant challenge.

Dietary Choices and Cancer

Food choices produce dietary patterns that may increase or decrease the risk of cancer (World Cancer Research Fund, 1997). A wealth of information shows that certain specific diets may offer protection against cancer at many sites. The challenge for nutritional science researchers is determining which BFCs, or combinations, are responsible for cancer protection or increased risk and for which cancer sites. The study of the American ("Western") diet and cancer risk has been ongoing for more than 4 decades, with important clues being discovered that suggest research pathways. For example, an analysis of prostate cancer among 3779 men in the NHANES Epidemiological Followup Study Cohort found three distinct dietary patterns in the United States: (1) a "vegetable–fruit" pattern that includes fish and shellfish; (2) a "red meat–starch" pattern that includes salty snacks, cheese, sweets, and desserts; and (3) a "Southern" pattern that includes traditionally Southern foods such as cornbread, grits, sweet potatoes, and okra (Tseng et al., 2004). The only dietary pattern associated with a decreased risk of prostate cancer was the "Southern" pattern (borderline significance), which was seen in both white and black men. Another prospective study of eating patterns and colon cancer found that a diet with high intakes of dietary fiber and folate was protective, especially among older Americans (Slattery et al., 1998). In the same study, a "Western" dietary pattern (high levels of red meat, processed meat, fast food, refined grains, and sugar-containing foods, and low levels of vegetables and fruits) was associated with an increased risk of colon cancer among men and women.

Aside from dietary patterns, a growing base of research exists that indicates specific types of foods or food constituents may reduce the risk of cancer. Table 2 lists selected nutrients that may modify cancer risk. The challenge for nutritional science is to confirm these findings in chemoprevention clinical trials and determine how they should fit into a diet that encourages improved health. Various food choices could satisfy the need for the particular BFCs associated with reduced cancer risk. For example, the carotenoid lycopene has been shown in animal and clinical studies to reduce the risk of prostate cancer by various mechanisms, including acting as an antioxidant, interfering with growth factor receptor signaling and cell cycle progression, and upregulating *connexin 43*, which allows direct intercellular gap junctional communication (Heber and Lu, 2002). A review of tomato products, lycopene, and prostate cancer risk found that eating one serving of lycopene-containing foods per day is associated with lower prostate cancer risk (Miller et al., 2002). In making food choices, lycopene is found in all tomato-based products regardless of processing, grapefruit, watermelon, papaya, and other fruits.

DISCOVERY

Discovery is the initial step in developing hypotheses that can be investigated in clinical investigations and intervention studies. Epidemiological and ecological studies provided clues for avenues of research for elucidating the diet–cancer relationship. In past decades, for example, comprehensive reviews of diet and cancer were published by the U.S. National Academy of Sciences (NAS) and the World Cancer Research Fund (WCRF) (NAS, 1982, 1989; WCRF,

TABLE 2 Selected Examples of Bioactive Food Components That May Modify Cancer Risk

Food source	Class of compound	Bioactive food component (s)
Cruciferous vegetables (arugula, Bok choy, broccoli, Brussels sprouts, cauliflower, collard greens, kale, mustard greens, radishes, rutabaga, turnips)	Isothiocyanate	Benzyl isothiocyanate, 2-phenethyl isothiocyanate, sulforaphane, allyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate
	Glycosinolate	Indole-3-carbinol, 3,3′-diindoylmethane, indole-3-acetonitrile
Vegetables	Minerals	Calcium, zinc, selenium
	Flavonoids	Quercetin, rutin
	Vitamins	Folic acid, vitamin A, vitamin E, vitamin C
Dark green vegetables (spinach, kale)	Carotenoids	Lutein
	Vitamins	Vitamin A, vitamin C
Vegetables, fruits, black tea	Flavonoid	Anthocyanins
Onions, garlic, scallions, chives	Allium compounds (Organosulfur compounds)	Diallyl sulfide, allylmethyl trisulfide, allyl mercaptan, *S*-allylcysteine
Citrus fruit	Flavonoid	Tangertin, nobiletin, rutin
Citrus fruit (peel), caraway seed oil	Terpenoid Monoterpenes	D-Limonene, perillyl alcohol, geraniol, menthol, carvone
Berries, tomatoes, potatoes, broad beans, broccoli, squash, onions	Flavonoid	Quercetin
Radish, horse radish, kale, endive	Flavonoid	Kaempferol
Tea, chocolate	Polyphenol	Epigallocatechin gallate, epigallocatechin, epicatechin, catechin
Grapes, red wine	Polyphenol	Resveratrol, catechin
Tumeric, curry, mustard fruits, coffee beans, soybeans	Polyphenol	Curcumin, caffeic acid
Strawberries, raspberries, blackberries, walnuts, pecans	Polyphenol	Caffeic acid, ferulic acid, ellagic acid
Cereals, pulses (millet, sorghum, soya beans)	Isoflavone	Genistein
Orange vegetables and fruit	Carotenoid	α- and β-carotene
Tomatoes	Carotenoid	Lycopene
Tea, coffee, cola, cacao (cocoa and chocolate)	Methylxanthines	Caffeine, theophylline, theobromine
Dairy products (milk, cheese, yogurt)	Vitamins	Vitamin D, calcium
Red meat	Vitamins	Iron

Source: Adapted from Manson (2003).

1997), among others. Based on substantive epidemiological and experimental evidence, these reviews indicate strong support for a diet–cancer relationship. In general, these reviews recommended increased intake of fiber and a variety of vegetables and fruits, moderate consumption of alcohol and salt, reduced fat intake, and increased physical activity. To illustrate, the WCRF reported that convincing evidence supported the hypothesis that a diet high in vegetables protects against cancers of the colon and rectum, stomach, lung, esophagus, mouth, and pharynx. Further, vegetables may protect against breast, bladder, pancreas, and larynx cancer, but the evidence was less convincing; and limited evidence suggests that vegetables reduced the risk of prostate, ovary, endometrium, cervix, liver, kidney, and thyroid cancers (WCRF, 1997). In addition, the WCRF proposed that dietary fat, excessive calories, obesity, and alcohol may increase the risk of cancer at various sites, whereas fruits, dietary fiber, and certain micronutrients may protect against cancer. Since the publication of the WCRF review, results from several large population-based epidemiological studies have been reported that provide additional clues to the relationship between nutrition and cancer.

Large-Scale Prospective Studies

Health Professionals Followup Study

The Health Professionals Followup Study (HPFS), begun in 1986 with follow-up in 1990 and 1994, is a prospective cohort study of 47,882 men in the United States that uses a validated 131-item semiquantitative food frequency questionnaire. HPFS analyses of dietary factors and prostate cancer suggests reduced risk with the intake of fish more than three times per week (Augustsson et al., 2003); equivocal findings for the intake of cruciferous vegetables, except for reduced risk among men younger than 65 years and those who reported higher intakes over the 10 years before baseline (Giovannucci et al., 2003a); reduced risk with higher intakes of fructose (>5 vs <1 servings per day) and increased risk with higher intakes of calcium (≥2000 mg/day vs

<500 mg/day) (Giovannucci et al., 1998a); and reduced risk among men younger than 60 years with a BMI ≥30 kg/m^2 compared with men with a BMI ≥23–24.9 kg/m^2 (Giovannucci et al., 2003b). A further analysis by Platz et al. (2003) found a direct association between energy intake and metastatic or fatal prostate cancer (but not prostate cancer incidence) among men who were lean, more physically active, and younger (≤65 years). The HPFS follow-up study will continue until 2007.

Nurses' Health Study

The Nurses' Health Study (NHS), begun in 1976, is a prospective follow-up study of 88,647 women and was originally designed to examine the relationship between contraception and breast cancer. The NHS-II, begun in 1989, was designed to include younger participants than the initial study and to focus on diet and lifestyle in cancer risk. Results of NHS-II and various nested case-control studies within the NHS have contributed important clues about the link between diet and cancer. Participants in the NHS completed a follow-up questionnaire every 2 years, and many of the questions pertained to nutrition and other lifestyle factors. Findings from the NHS indicate that there may be an inverse association between vegetable fat, eggs, and fiber intake and breast cancer (Frazier et al., 2003); fruit and vegetable intake and lung cancer (Feskanich et al., 2000) and colon and rectum cancer (Michels et al., 2000); red meat and all meat and invasive breast cancer (Holmes et al., 2003); folate and colon cancer (at 15 years of follow-up but not at 5 years of follow-up) (Giovannucci et al., 1998b); and folate and hyperplastic polyps of the colon and rectum (Kearney et al., 1995). Direct associations between diet and cancer in the NHS were reported for intake of animal protein and invasive breast cancer (Holmes et al., 2003); alcohol and hyperplastic polyps of the colon and rectum (Kearney et al., 1995); and butter and breast cancer (Frazier et al., 2003). The NHS-II inquired about diet during adolescence of the participants and found inverse associations between vegetable fat, vitamin E, and fiber intake and proliferative benign breast disease (Baer et al., 2003), as well as carbohydrate intake among women with BMI <25 kg/m^2 (Cho et al., 2003). Direct associations in the NHS-II included total animal fat, animal fat, and monosaturated fats, and proliferative benign breast disease (Baer et al., 2003), as well as carbohydrate intake among women with BMI ≥25 kg/m^2 (Cho et al., 2003).

Cancer Prevention Study II Nutrition Cohort

The Cancer Prevention Study II (CPS-II) is a prospective study of cancer incidence and mortality; the Nutrition Cohort is a subgroup of ~86,000 men and 98,000 women from the 1.2 million CPS cohort identified in 1982. Compared with baseline (1992) intakes of whole grains, fruits, and vegetables, results of a 5-year follow-up study indicated that men with the highest vegetable intake had a nonsignificant 30% reduction in risk of colon cancer; men at the lowest quintile of intake of vegetables and fiber had significantly (vegetables RR = 1.79; fiber RR = 1.96) increased risk (McCullough et al., 2003). In addition, women at very low intakes of fruit were at increased risk (RR = 1.86) for colon cancer. Another analysis from CPS-II indicated that postmenopausal women who had gained >70 pounds since age 18 years had double the risk of breast cancer compared with women who had maintained their weight within 5 pounds of their weight at age 18 years (Feigelson et al., 2004).

European Prospective Investigation into Cancer and Nutrition (EPIC)

The EPIC study, the largest study of diet and health ever undertaken, was initiated in 1992 to collect information from >520,000 people in 10 European countries. Recruitment was completed in 1999, and follow-up will continue for 10 years (Riboli and Kaaks, 1997). Preliminary results support the conclusion that increased intakes of fruits and vegetables reduce the incidence of cancers of the colon and rectum and upper aerodigestive tract; preliminary results do not support the protective effect previously found for cancers of the stomach and lung, although this may be due, in part, to the brief follow-up period (Riboli and Lambert, 2002). Other findings include an increase in colon cancer risk with consumption of preserved meats, as well as a significant reduction in colon cancer risk with fish consumption. EPIC also has collected blood samples from most participants for investigations of biomarkers of dietary intake (e.g., levels of vitamins), biomarkers of diet-related factors (e.g., indicators of antioxidant status), and markers of hormones that can be influenced by diet and may be associated with cancer risk (Riboli and Kaaks, 1997).

Black Women's Health Study

The Black Women's Health Study (BWHS), begun in 1995, enrolled 64,500 women in a cohort to assess all aspects of health, including diet, obesity, alcohol consumption, and physical activity, with a focus on breast cancer. This long-term prospective study is collecting data on energy, total fat, saturated fat, protein, carbohydrate, dietary fiber, calcium, iron, vitamin C, folate, β-carotene, and vitamin E using dietary recall, food-frequency questionnaires (FFQs), and daily diaries (Kumanyika et al., 2003). Results will be reported periodically as follow-up data are collected.

Immigrant Studies on Diet and Cancer

Comparison of cancer rates among immigrants in their host country with those in their country of origin has provided important clues to the role of environmental factors in cancer etiology. One of the earliest population-based studies compared gastrointestinal and colon cancer rates, which are related to diet, in the San Francisco area among Japanese, Japanese immigrants, and Japanese Americans (U.S. born) (Dunn, 1977). For gastric cancer, which has a high rate in Japan and low rate in the U.S. population, a stepwise reduction in rates was seen when comparing Japanese rates, rates among Japanese immigrants, and U.S.-born Japanese Americans. For colon cancer, which has a low rate in Japan and a high rate in the U.S. population, a stepwise increase in rates was seen when comparing Japanese rates, rates among Japanese immigrants, and U.S.-born Japanese Americans. A similar pattern of changes was seen for breast, uterine corpus, and ovarian cancer among immigrant women and for prostate cancer rates among immigrant men (Dunn, 1977). A population-based study in Los Angeles of Japanese, non-Spanish–surnamed white, and Spanish-surnamed white immigrants found prostate and breast cancer incident rates were higher than those in homeland populations and approached U.S. rates the longer the immigrant resided in this country (Shimizu et al., 1991). A study in Illinois that investigated the role of acculturation among Mexican and Puerto Rican immigrants indicated that cancer rates for immigrant Puerto Rican males was closer to U.S. rates than for either Puerto Rican females or Mexicans (Mallin and Anderson, 1988). Overall, these results suggested that the quicker an immigrant group becomes acculturated to the host country lifestyle, the quicker the immigrant population transitions to the cancer rates of the host country.

A unique opportunity for nutrition discovery research in an immigrant population is the investigation of cancer rates among the Hmong population, an agrarian people from the mountainous regions of Vietnam, Cambodia, and Laos. The Hmong immigrated to the United States after the Vietnam War, and the U.S. population of Hmong is ~100,000. Population studies in California and Minnesota, where a majority of Hmong immigrants settled, indicate that baseline cancer rates reflective of those from their host country show elevated rates for cancers of the nasopharynx, stomach, liver, pancreas, leukemia, and cervix, as well as non-Hodgkin's lymphoma, and lower rates for cancers of the breast, prostate, and colon/rectum (Mills and Yang, 1997; Ross et al., 2003). This cancer profile is characteristic of rates seen when comparing developing and developed countries. Among the Hmong, cancer rates will be systematically investigated over time not only to determine whether cancer rates become synchronized with U.S. rates, but also to assess which interventions may succeed in interrupting the synchronization. Dietary changes during acculturation will be investigated to assess the role of diet in cancer risk. A study of food habits and food consumption patterns has shown that adult Hmong prefer to maintain strong ties to their native foods and traditional diets, but Hmong adolescents prefer both American and native foods (Story and Harris, 1989). The effect of genetic differences also will be investigated. For example, genotyping studies have found significant differences between the Hmong population and U.S. whites, including significantly lower frequencies of the glutathione *S*-transferase μ1 (GSTM1) and glutathione *S*-transferase theta1 (GSTT1) genes among the Hmong (Kiffmeyer et al., 2004). This information may suggest possible interventions to cancer researchers, including future genetic or proteomic interventions, to reduce cancer risk and increase survival.

Evidence from Animal Models

Animal models offer unique opportunities for discovery related to the process of carcinogenesis, the role of gene–environment interactions, and potential chemoprevention strategies associated with diet and nutrition. Most models for nutrition research assess exposure to specific dietary factors in mice and rats with a predetermined susceptibility to specific types of cancer. These models use tumor development or preneoplastic biomarkers in animals with overexpressed or underexpressed genes as endpoints, often with exposure to exogenous carcinogens such as azomethane (AOM). For example, a review of dietary chemoprevention studies in AOM-induced *Min* mice and other mice with mutations resulting in intestinal tumors found that resveratrol, fish oil, curcumin, folic acid, and caffeic acid phenethyl esters reduced tumor yield by 60–70% (Corpet and Pierre, 2003). This review indicated that similar results occurred in AOM-induced rats. Curcumin also has been shown to reduce the development of adenomas in C57B1/6J *Min*/+ mice, developed as a model for human familial APC (Perkins et al., 2001). In this study, curcumin at 0.1% in the diet had no effect; at 0.2 and 0.5%, however, adenomas were reduced by 39 and 40%, respectively, compared with untreated mice, suggesting that the dose of an agent is important to achieve maximum chemopreventive effect (Perkins et al., 2001). Studies in AOM-induced rats have suggested that almonds and almond fractions reduce aberrant crypt foci in F344 male rats (Davis and Iwahashi, 2001), and dietary whey protein reduces the incidence, though not number or mass, of colon tumors in male offspring of female Sprague–Dawley (S-D) rats (Hakkak et al., 2001). *N*-methyl-*N*-nitrosourea (NMU)–induced mammary tumorigenesis in S-D rats has been reported to be significantly reduced by a diet high in flaxseed, the richest source of plant-based omega-3 fatty acids and dietary lignans, and secoisolariciresinol diglycoside (SDG), a major precursor of mammalian lignan, compared with rats fed a diet lower in these components

(Rickard et al., 1999). Mammary tumorigenesis in S-D rats also is inhibited by exposure to either flaxseed or SDG during suckling (Chen et al., 2003). Male Wistar–Unilever rats treated with NMU and testosterone had a statistically lower risk of dying from prostate cancer on a diet of tomato powder (hazard ratio [HR] = 0.74) or on energy-restricted diets (HR = 0.68) than rats fed diets high in lycopene or *ad libitum* diets (Boileau et al., 2003). Energy (caloric) restriction has been shown to be a viable cancer prevention strategy in several animal models. For example, a review of studies using caloric restriction for spontaneous mammary tumors in various strains of mice found a 55% reduction in mammary tumors in energy-restricted animals compared with controls, regardless of the nutrients used in the studies (Dirx et al., 2003). In addition, a 40% energy-restricted diet in August Copenhagen Irish (ACI) rats treated with 17-estradiol (E2) inhibited mammary carcinogenesis, partly by slowing the progression of atypical hyperplastic foci to carcinoma (Harvell et al., 2001).

The growth of investigations using transgenic animal technology has been significant in the past decade. Transgenic murine models provide insight into mechanisms that contribute to the carcinogenic process. For example, mice develop prostate cancer spontaneously at puberty in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model. Dietary genistein, at levels comparable with those in Asian men on their regular soy diet, significantly reduced the development of prostatic adenocarcinoma in a dose-dependent manner in the TRAMP model (Mentor-Marcel et al., 2001). In addition, the polyphenolic fraction of green tea (GTP) fed to TRAMP mice at a human-equivalent dose of 6 cups of tea/day significantly inhibited prostate cancer development, progression, and metastasis (Gupta et al., 2001).

TRAMP mice fed a diet containing flaxseed for 30 weeks had significantly less aggressive prostate tumors than control mice (Lin et al., 2002). A transgenic murine model also has been developed to investigate the effect of estrogen, antiestrogens, and isoflavones in modifying mammary growth, tumor development, and phenotypic aggression. Female FVB/N-TgN (MMTV-*neu*) transgenic mice were fed a soy-based diet; control mice were fed a casein-based diet (Yang et al., 2003). The FVB mice failed to develop mammary tumors, suggesting that in this *Wt-erbB*-2 transgenic mouse model, tumor development was specifically associated with the transgene. In addition, short-term tamoxifen use at an early stage of development blocked tumor development in 80% of the mice (Yang et al., 2003).

Molecular Targets in Nutrition

To address one of the most compelling questions in nutritional oncology—How does food interact with cellular structures and biological processes to affect genotypic and phenotypic changes?—research has become increasingly more focused on exploring molecular targets of BFCs. Molecular targets may be individual genes, molecules that either result from gene expression or are otherwise affected by gene expression, or any other molecular events that are relevant to the process of carcinogenesis (Milner et al., 2001b). Molecular targets related to cancer risk have been identified and are associated with various nutrients, including vitamin D, calcium, folate, selenium, genistein, and resveratrol (reviewed in Milner et al., 2001b). These nutrients act through various processes to influence hormonal regulation, cell signaling, cell cycle control, apoptosis, differentiation, or carcinogen metabolism. Selenium provides an example of progress being made in understanding the role of molecular targets in nutrition and cancer risk.

Dietary selenium primarily is found in vegetables and fruits, although the amount provided is highly dependent on the soil content. Selenium has been shown to have reduced cancer risk through numerous mechanisms, which include acting as an antioxidant, suppressing cell proliferation, enhancing immune response, altering the metabolism of carcinogens, and inducing apoptosis (reviewed in Fleming et al., 2001). Selenium imposes its biological activity through its numerous compound forms, mainly selenoproteins, which influence various molecular targets and pathways (Ip, 1998). As an antioxidant, selenium takes part in the thioredoxin system, acting as a constituent of the selenoenzyme thioredoxin reductase (TR). TR reduces thioredoxin, which causes reduced activity of nuclear transcription factor-κB (NFκB) activation, an inducible oncogenic factor that causes induction of genes involved in a number of physiological processes, including those associated with cytokines, growth factors, cell adhesion molecules, and immunoreceptors (Milner et al., 2001b). To illustrate, a direct genetic effect of selenium is the inhibition of DNA synthesis and induced DNA strand breakage by increasing cdc2/cdk2 kinase activities and arresting cell growth in $S/G_2/M$ (Sinha et al., 1996). Additionally, selenium is involved in influencing apoptosis by *fas* ligand and *p38* stress kinase induction (Fleming et al., 2001). A study in *Min* mice fed selenium-enriched broccoli investigated gene expression in the mouse liver (Zeng et al., 2003). Results indicated that selenium-enriched broccoli enhanced the binding of transcription factor p53, NFκB, and AP-1 to their *cis*-acting elements, thus reducing tumorigenesis.

Systematic Approach for Biomarkers in Nutrition Research

Discovery in nutrition research through the identification, validation, and application of biomarkers is an emerging strategy for cancer prevention and intervention. Biomarkers are defined as cellular, biochemical, molecular, or genetic alterations that can be recognized or monitored and can be

assessed from tissues, cells, or fluids (Verma and Srivastava, 2003). Biomarkers are investigated in nutritional oncology to determine exposure (intake) to BFCs, to assess the response of molecular processes and pathways after exposure to BFCs, to elucidate susceptibility of individuals to specific exposures, and as surrogate endpoints in clinical studies of dietary factors or nutrient-related chemopreventive agents (Srivastava and Gopal-Srivastava, 2002). The National Cancer Institute's (NCI) Early Detection Research Network (EDRN) has initiated a systematic approach for biomarker research that includes the integration of discovery, evaluation, and validation of biomarkers. Detailed information on this approach may be found at the EDRN web site at http://edrn.nci.nih.gov. The use of biomarkers in nutrition represents a considerable challenge because diet-related cancers develop over long periods of time, and changes at the molecular level caused by BFCs appear to be small, with the possible accumulation of these small changes over time being responsible, at least in part, for increases in cancer risk (reviewed in Branca et al., 2001). There are few validated biomarkers for exposure to BFCs or for the effect of BFCs on cancer susceptibility related to diet.

Serum biomarkers have been used for decades to assess dietary intake and to validate information provided on FFQs or other methods for determining dietary habits (Crews et al., 2001). For example, in a study of Michigan breast cancer patients, the Healthy Eating Index (HEI), an analytical measure of compliance with the U.S. Department of Agriculture (USDA) dietary guidelines for daily food consumption, was compared with plasma biomarkers for carotenoids, folate, and vitamin C (Hann et al., 2001). Results indicated that significant correlations existed between HEI scores and biomarkers for carotenoids, except lycopene, and for vitamin C. Serum carotenoids also have been investigated recently in the New York Women's Health Study as a biomarker of fruit and vegetable consumption, with moderate success (van Kappel et al., 2001).

Using biomarkers to identify gene-specific mutations has promise for understanding specific interactions between dietary factors and genetic or epigenetic processes. For example, oxidative DNA damage assessed by 8-hydroxy-2-deoxyguanosine (8OHdG) and the Single Cell Gel Electrophoresis Assay (Comet assay) has been investigated in dietary intervention studies to examine the role of dietary and supplemental antioxidants (Møller and Loft, 2002). They reviewed single-dose, multiple-dose, and natural food product studies and determined that antioxidants generally reduce both 8OHdG concentrations and DNA strand breaks, but variability of study design, length of exposure, and method of assessment differed among studies, making clear associations difficult.

Gene expression profiles have been made possible by the application of emerging technologies in nutritional sciences. The ability to analyze expression patterns of thousands of genes simultaneously is possible by using high-throughput tools such as microarray and chip technology. A study using an oligonucleotide array found that selenium, when added to a culture of synchronized human prostate cells, influences many genes and presents a distinct pattern of expression (Dong et al., 2003). Expression profiles also can be used to determine the effect of BFCs on methylation. Abnormal methylation patterns are almost universally associated with cancer and dietary factors such as folate, choline, and vitamins B6 and B12 limit the availability of methyl groups for DNA methylation (Milner, 2003).

Because nutrition does not generally cause major changes in gene expression, it is important to investigate the many minor changes that occur through nutrient and nonnutrient exposure related to diet. By integrating studies of genomics (the study of genes and their functions), proteomics (the study of protein shape, function, and patterns of expression), and metabolomics (the study of low-molecular-weight fractions of cells, tissues, and body fluids) to identify valid biomarkers associated with the actions of BFCs, the new paradigm for nutritional science may be realized. For example, the use of chromatographic separation technology in a metabolomic study of rats found that >250 diet-dependent compounds could be identified in plasma, which may allow them to be used as biomarkers for the identification of metabolomic genotypes and phenotypes associated with health or disease (Watkins and German, 2002). Proteomic technology has been used to investigate potential prostate cancer biomarkers. Using surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectometry, Zheng et al. (2003) found a protein (PCa-24) present in 16 of 17 prostate carcinoma specimens that may be a potential biomarker for this condition; PCa-24 was not expressed in any of the 12 benign prostatic hyperplasia specimens studied. With the human genome completely sequenced and our improved understanding of the proteins and metabolites involved in gene–nutrient interactions, the challenge for nutrition researchers is to assimilate knowledge from all fields to identify and validate biomarkers that signify changes from good health to clinical cancer.

DEVELOPMENT

Development of nutritional interventions within the 3-D approach to cancer prevention is based on the evaluation of findings from discovery that show promise for reducing the cancer burden (von Eschenbach, 2003). Nutritional components have been under investigation at the NCI for more than 2 decades. Table 3 presents information on selected nutritional components being investigated in NCI chemoprevention trials. Phase I clinical trials are designed to determine the dose-related safety and toxicity of the proposed chemopreventive agent. Phase II clinical trials evaluate agent

TABLE 3 Selected NCI-Sponsored Phase I: II: and III Cancer Prevention Trials of Nutritional Factors

Cancer site	Phase I	Phase II	Phase III
Breast	Soy isoflavones Indole-3-carbinol[b]	EGCG/polyphenon E (green tea extract)	
Colon	Curcumin	Folic acid[a] (2 trials) Vitamin D[a]/calcium	
Lung	*l*-Selenomethionine/vitamin E		Selenized yeast 13-*cis*-retinoic acid[b]
Prostate	Lycopene (3 trials) Soy isoflavones Genistein[b]	Selenized yeast Soy (dietary) Soy isoflavones Vitamin D analogue Selenium[a]	Selenomethionine Selenium/vitamin E [a]Diet low in fat and high in soy, fruits, vegetables, green tea, vitamin E, and fiber
Cervix		9-*cis*-Retinoic acid β-carotene[b]	Folic acid[a]
Bladder			High-dose multivitamins[a]
Anogenital warts + HPV/HIV		Indole-3-carbinol	
Skin	EGCG/polyphenon E (Green tea extract)	Retinol,[a] Retinyl palmitate EGCG[a]/polyphenon E (Green tea extract)	
Head and Neck			β-carotene[a] 13-*cis*-retinoic acid[a] (2 trials)

[a]Accrual completed; study closed to new participants.
[b]Completed.
EGCG, epigallocatechin gallate (polyphenon E).

efficacy in a larger group of participants at high risk for specific cancers and can provide data that characterize dose, safety, and toxicity in the selected population. Phase III clinical trials are randomized, double-blinded, placebo-controlled trials conducted in a large population of participants. Phase III trials have well-defined primary, and often secondary, endpoints that allow investigators to determine the agent's usefulness as a prevention or treatment strategy for a specific cancer type. Development with phase III clinical trials also includes large-scale dietary modification trials that investigate the effect of selected BFCs or groups of BFCs on cancer risk. Modification trials generally have endpoints that address changes in lifestyle, reducing the levels of some dietary factors or increasing others. These trials also offer the opportunity to investigate the overall diet for its effect on biomarkers of exposure and susceptibility.

Large-Scale Phase III Chemoprevention Trials

Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Selenium has been extensively studied in experimental models and has been found to reduce cancer risk through numerous mechanisms, including antioxidant effects, enhancement of immune function, induction of apoptosis, inhibition of cell proliferation, alteration of carcinogen metabolism, cytotoxicity of metabolites, and influence on testosterone production (reviewed in Klein, 2004). SELECT was designed to further clarify findings from previous population-based trials that reported on the possible benefits of selenium and vitamin E. For example, a population-based clinical trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) found in a secondary analysis that men receiving vitamin E had a decrease in prostate cancer mortality (41%) and incidence (36%) (Heinonen et al., 1998). In addition, secondary analysis of the HPFS found that daily use of vitamin E (100 μg/day) decreased the risk of metastatic or fatal prostate cancer 44% compared with nonusers (Chan et al., 1999). Secondary endpoint analyses from a multicenter, double-blind, randomized, placebo-controlled cancer prevention trial indicated that supplemental dietary selenium (200 μg/day) significantly reduced the risk of total cancer mortality by 50% (Clark et al., 1996) and prostate cancer incidence by 63% (Clark et al., 1998). In addition, the Nutrition Intervention Trial in Linxian, China, in a region of low selenium levels in the soil and food, found significant inverse associations between baseline serum selenium and death from esophageal (17% reduction) and gastric cancers (25% reduction) (Wei et al., 2004).

Given these encouraging results, the NCI sponsored SELECT, a randomized, prospective, double-blind study, to

determine whether daily supplementation of selenium and vitamin E will decrease the risk of prostate cancer in healthy men (Klein et al., 2001). SELECT is a four-arm intervention trial comparing vitamin E alone (400 mg of racemic α-tocopherol), selenium alone (200 μg of 1-selenomethionine), combined vitamin E and selenium, and placebo. The trial is scheduled to provide a 7- to 12-year regimen that includes an optional multivitamin that does not contain selenium or vitamin E. Routine clinical evaluations will include a yearly digital rectal examination and prostate-specific antigen test. SELECT is the largest prostate prevention trial ever conducted, and as of January 2004, ~90% of the targeted goal of 32,400 men had been enrolled. The primary endpoint is diagnosed prostate cancer; secondary endpoints will be the incidence of and survival from lung and colon cancers.

An important role for SELECT in the development of selenium as a chemopreventive agent is the inclusion of a biomarker study within the trial. A nested case-control study within SELECT will assess genetic polymorphisms of four genes, androgen receptor (*AR*), 5α-reductase type II (*SRD5A2*), cytochrome P450*c* 17α (*CYP17*), and β-hydroxysteroid dehydrogenase (*HSD3β2*), on prostate cancer incidence (Hoque et al., 2001). Substantial discovery efforts involving epidemiological and experimental studies suggest that these biomarkers of risk may affect susceptibility to prostate cancer (Haiman et al., 2001). For example, experimental studies have shown that selenium induces growth inhibition in human prostate cancer cell lines, but only if the cells have a functioning AR (Venkateswaran et al., 2002). Knowing whether the mechanisms of selenium action are dependent on specific AR polymorphisms could assist researchers in developing more specific preventive strategies for populations affected by the relevant AR polymorphisms. In addition, polymorphisms in *CYP17* A1/A1 genotype may confer a significantly higher serum androgen level, which is associated with higher risk of prostate cancer than found in men with either the A1/A2 or A2/A2 genotype (Hoque et al., 2001).

Physicians' Health Study-II

The Physicians' Health Study-II (PHS-II) was designed after the end of PHS-I in 1995, which did not support either benefit or harm from 12 years of β-carotene supplementation on the primary prevention of cancer and cardiovascular disease; the aspirin component of PHS-I was stopped early because of the benefit of aspirin on the risk of a first heart attack (Hennekens et al., 1996). PHS-II is a randomized, double-blind, placebo-controlled trial to investigate the role of vitamin C, vitamin E, β-carotene, and a multivitamin for the primary prevention of total cancer, prostate cancer, and cardiovascular disease (Christen et al., 2000). The trial uses a $2 \times 2 \times 2 \times 2$ factorial design and is the only trial testing the potential benefits of vitamin E in the prevention of prostate cancer and β-carotene on prostate and total cancer; in addition, it is the only primary prevention trial in healthy men testing multivitamins or any single antioxidant vitamin, alone or in combination, on cancer and CVD (Christen et al., 2000). Follow-up is scheduled to begin after 5 years.

Trials of β-Carotene

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) and the Beta-Carotene and Retinol Efficacy Trial (CARET) have been controversial for the surprising finding that β-carotene was associated with an increased risk of lung cancer among smokers (ATBC Group, 1994; Albanes et al., 1996; Omenn et al., 1996). Both trials were conducted in cigarette smokers, with a 16% increase in lung cancer in the β-carotene group of the ATBC Study and a 28% higher incidence of lung cancer in participants receiving the β-carotene/retinyl palmitate combination in CARET. The ensuing international controversy surrounding these findings has been reviewed by Greenwald (2003); potential issues included dose, timing of the dose, interference by β-carotene in absorption of other carotenoids or antioxidants, and the duration of the studies. Subsequent investigations and reviews have added important information to this controversy. A postintervention follow-up of the ATBC Study found that the beneficial effects of vitamin E (α-tocopherol) and the negative effects of β-carotene disappeared after 4 years postintervention (Virtamo et al., 2003). The authors, representing the ATBC Study Group, continued their recommendation that smokers avoid β-carotene. The *Pooling Project of Prospective Studies of Diet and Cancer* analyzed data from seven cohort studies (~400,000 participants and 3150 cases) of dietary carotenoids and lung cancer (including the ATBC Study) and found that intakes of β-carotene, α-tocopherol, lutein/zeaxanthin, and lycopene were not associated with lung cancer risk (Männistö et al., 2004). Of the carotenoids studied, only β-cryptoxanthin was significantly inversely associated with lung cancer risk.

Large-Scale Dietary Modification Trials

Polyp Prevention Trial

The Polyp Prevention Trial (PPT) is a multicenter, randomized, controlled dietary intervention trial that is examining the effect of a low-fat (20% of calories from fat), high-fiber (18 g/1000 calories), high-vegetable and -fruit (five to eight daily servings, combined) dietary pattern on the recurrence of adenomatous colorectal polyps (APC) (Lanza et al., 1996; Schatzkin et al., 1996). Participants received extensive dietary and behavioral counseling on how to meet dietary goals. Results reported by Shatzkin et al. (2000) indicated that the PPT dietary intervention did not

influence the risk of recurrence of APC. A subsequent analysis, however, did show that study participants in the intervention arm of the PPT made sustained significant changes in all PPT goals: reduced fat intake and increases in fiber and fruits and vegetables (Lanza et al., 2001). Intervention participants also reported significantly higher serum carotenoid concentrations and lower body weights than the control group. This finding is of particular importance to cancer prevention researchers as further preventive dietary interventions are designed.

Women's Health Initiative

The Women's Health Initiative (WHI), which began in Fall 1993, is a 15-year, multidisciplinary trial that includes both dietary and chemopreventive interventions. The nutritional components of the WHI include the Low-Fat Dietary Modification Trial (20% of calories from fat) and the Calcium/Vitamin D Supplementation Trial (calcium and vitamin D supplementation) for prevention of cancer, cardiovascular disease, and osteoporosis. A separate WHI initiative on hormone replacement therapy (estrogen plus progestin) was stopped in 2002 because of results indicating an increase in invasive breast cancer (Rossouw et al., 2002). Although disease endpoints are not complete for the nutritional components of the WHI, observational studies suggest that behavioral interventions designed for this trial have resulted in significant dietary changes, especially regarding reduced fat intake (Patterson et al., 2003).

Women's Healthy Eating and Living Study

The Women's Healthy Eating and Living (WHEL) Study, which began in 1996, is a multicenter, randomized dietary intervention trial among breast cancer survivors. The study is investigating the effectiveness of a high-vegetable, low-fat diet in reducing additional breast cancer events and early death in women within 4 years of diagnosis of early-stage invasive breast cancer (Pierce et al., 2002). An important aspect of the study is to investigate the impact of raising circulating carotenoid concentrations through changes in diet. Preliminary results have assessed the methods used in WHEL (FFQ, 24-hour dietary recall, intensive telephone counseling, cooking classes, and print materials) and found that the use of a multimodal, multimethod intervention is beneficial for promoting dietary change (Thomson et al., 2003). The study is scheduled for completion in 2006.

DELIVERY

Delivery is the process of disseminating, facilitating, and promoting evidence-based prevention, detection, diagnosis, and treatment practices and policies to reduce the burden of cancer in all segments of the population (von Eschenbach, 2003). A primary focus of these efforts is to develop strategies for those populations who bear the greatest burden of disease. Delivery works most efficiently when it is part of the processes of "Discovery" and "Development." SELECT is an excellent example of an integrated 3-D approach. Coordinated by the Southwest Oncology Group (SWOG), SELECT includes >400 study sites throughout the United States, Puerto Rico, and Canada. SWOG and many of the other study sites belong to the NCI's Community Clinical Oncology Program (CCOP), which is a creative mechanism designed to improve the accrual of patients to NCI phase III clinical trials while encouraging community-based oncologists to participate in clinical research. In addition, CCOP is one of the most practical means to disseminate new information on state-of-the-art cancer treatment outside the traditional cancer centers and research-oriented medical centers (Kaluzny et al., 1989). Clinicians and the public will receive immediate access to the prevention and treatment strategies that are most relevant to their communities because local researchers and facilities will be developing and participating in research translation efforts at the community level. For example, African American men and those in lower socioeconomic strata (SES) have the highest rates of prostate cancer, with race and SES being independent predictors of stage at diagnosis (Schwartz et al., 2003). Prevention and treatment strategies in SELECT can be immediately integrated and delivered in those CCOP communities that include populations that may benefit the most from intervention.

Understanding the most efficient and successful nutritional strategies to support cancer prevention, screening, and treatment for those individuals or groups that will benefit the most is a significant challenge for cancer researchers. The small and large hospitals, private practices, and groups of organizations or private practices that compose the CCOP network have been invaluable in creating the environment for research translation to health professionals and the public. CCOP includes 51 centers in 34 states, the District of Columbia, and Puerto Rico, as well as 11 Minority-Based CCOP Programs (MB-CCOP) that serve a large population of minorities. The network provides access to cancer clinical trials in 403 community-based hospitals, with >4000 community physicians participating in NCI clinical trials through this network (CCOP web site, 2003). Many of these clinical trials, such as SELECT, are investigating chemoprevention agents that include natural or synthetic nutritional components and contain programs for dissemination.

Challenges in Delivery for Nutritional Oncology

A significant challenge in delivery is determining the benefits within a population of dietary changes and whether

lifestyle changes per se offer a greater benefit than treatment, screening, or chemoprevention. The analysis of worldwide cancer incidence and mortality rates mentioned previously confirms that diet influences cancer (Young and LeLeu, 2002), although changes in lifestyle generally take many years to accrue benefits compared with the shorter-term benefits of using treatment or chemoprevention approaches. Risks of treatment or chemoprevention, which are higher than dietary interventions, also must be considered when deciding whether lifestyle approaches should be implemented, especially as nutritional oncology appears to be in a transition period emphasizing the integration of lifestyle and medical approaches to cancer prevention. These issues must be weighted carefully in recommendations for lifestyle or medical approaches.

Medical Education

Delivery of evidence-based practices for the benefit of those most at risk for cancer will depend on improving nutrition education for clinicians and application of proven interventions and programs at the community level. Assessments indicate a lack of time spent on nutrition in our medical training institutions. A survey of medical schools in the United States found that nutrition medical education was required in only ~20% of the programs (Touger-Decker, 2004). A survey of hours of nutrition education in medical schools found that medical schools have an average of only 18 hours of instruction over a 4-year program (Torti et al., 2001). Improving nutrition medical education can encourage delivery of diet-related research results and help integrate delivery into the new nutrition paradigm. There have been calls to provide an integrated nutrition education message within every aspect of medical education so that graduates enter practice with an understanding of the integral role of nutrition in health and disease (Kushner, 2002).

Nutrition Policy

The awareness of the role of nutrition in cancer prevention should be integrated into all policies at the national, state, and local levels. In the past decade, with the maturity of electronic communications systems such as the Internet, cable TV, and home personal computing, information is becoming increasingly more available at every stratum of the population. The same media that bring information to the consumer, however, also bring conflicting information on the role of nutrition and specific diets in maintaining health. The USDA and the U.S. Department of Health and Human Services have the primary role for providing nutrition education and advice at the national level. Development of the Food Pyramid, and subsequent revisions, has provided consumers with science-based information on appropriate food choices. An interactive USDA web site (http://www.mypyramidtracker.gov) allows individuals to assess their diets in context of the amount of physical activity they perform and to set goals for maintaining or losing weight. This type of service adds to the knowledge of those who choose to participate. The movement of policymakers at the national level toward evidence-based national dietary guidelines is promising (Cooper and Zlotkin, 2003).

Application of nutrition-based policy is exemplified by the 5 A Day For Better Health Program (5 A Day), which was begun by the NCI in 1991 but was transferred to the Centers for Disease Control and Prevention. The 5 A Day Program is a cooperative initiative between the federal government and the vegetable and fruit industry to increase the intake of vegetables and fruit to reduce cancer risk. An evaluation of the 5 A Day program indicated that implementing a media campaign, point-of-purchase initiatives, such as use of the "5 A Day" logo on products, and community-level interventions have significantly increased intake from 1991 to 1997 (Stables et al., 2002). The 5 A Day program evaluation report and more about the program can be found by visiting their web site at http://www.5aday.gov/.

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