CHAPTER

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Dietary Supplements in Cancer Prevention and Therapy

MARY FRANCES PICCIANO, BARBARA E. COHEN, AND PAUL R. THOMAS

INTRODUCTION

Dietary supplements are regulated in the United States by the Food and Drug Administration (FDA) under authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). An amendment to the FFDCA, the Dietary Supplement Health and Education Act of 1994 (DSHEA), defines a dietary supplement as a product that is intended to supplement the diet and contains at least one or more of certain dietary ingredients, such as a vitamin, mineral, herb or other botanical, or an amino acid. These products may not be represented as conventional foods and are marketed in forms that include capsules, tablets, gelcaps, softgels, and powders. Although manufacturers are required to have evidence to support their claims of a dietary supplement's safety and efficacy, FDA approval is not required before a product is marketed.

The passage of DSHEA played a role in increasing the use of supplements in the United States by ensuring consumer access to a wide range of such products (U.S. Congress, 1994). The legislation also created the Office of Dietary Supplements within the National Institutes of Health (NIH) with the mission "to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population" (Office of Dietary Supplements, 2004).

Dietary supplements are commonly purchased and consumed in the United States even though they may not have proven benefits for the general population and, for some, may have harmful effects. However, the possibility that supplements help to prevent cancer development, progression, or reoccurrence attracts many people. A rigorous approach must be taken to determine the circumstances under which dietary supplements may have beneficial health effects on cancer or on any other disease or medical disorder. Special attention must be given to the circumstances that could influence the effects of dietary supplements, including the timing of supplement use, dose and dose–response, the role of specific supplement components, and the impact of interactive factors. This chapter addresses these issues with selected examples. Although it is beyond the scope of this chapter to address these issues for all supplements, the points made here are relevant to almost all categories of dietary supplements.

PREVALENCE OF DIETARY SUPPLEMENT USAGE AMONG PEOPLE WITH CANCER AND THE GENERAL POPULATION

As many people are motivated to change their food-intake behaviors with the hope of improving their health, they also are using a variety of alternative strategies including the consumption of vitamin, mineral, herbal, and botanical supplements (Halsted, 2003). The following two subsections present the most recent data on the prevalence of and reasons for dietary supplement use, first in the general population and then among people diagnosed with cancer.

Dietary Supplement Use in the General Population

Data from the latest National Health and Nutrition Examination Survey (NHANES) indicate that 52% of the U.S.

adult population took some sort of dietary supplement in 1999–2000, most commonly a multivitamin and multimineral supplement (35%) (Radimer et al., 2004). The 1987 National Health Interview Survey (NHIS), conducted by the Centers for Disease Control and Prevention, found that 51.1% of U.S. adults used a vitamin or mineral supplement, but only 23.1% on a daily basis (Subar and Block, 1990). The daily use of vitamin or mineral supplements increased to 33.9% in the 2000 NHIS, and 6% of the respondents reported using nonvitamin or nonmineral supplements (Millen et al., 2004). The 2002 NHIS indicated that 38.2 million American adults (~19%) use nonvitamin nonmineral supplements, primarily botanical products (Barnes et al., 2004). Market data show that in 2004 the sale of vitamins, herbs and botanicals, sports nutrition supplements, minerals, meal supplements, and other specialty supplements totaled $20.33 billion, representing a $4.27 billion (26.6%) increase since 1999 (*Nutrition Business Journal*, 2005). The 2004 sales of vitamins and minerals, in either a multivitamin-multimineral or single-nutrient form, were 42% of all sales ($8.63 billion).

Data from NHANES and other research efforts have also been useful in identifying characteristics of supplement users and the reasons for supplement use. These findings indicate that the highest usage of vitamin and mineral supplements is associated with being female, having an education beyond high school, having a higher income, being non-Hispanic white, and being older (Steward et al., 1985; Koplan et al., 1986; Medeiros et al., 1989; Moss et al., 1989; Subar and Block, 1990; Bender et al., 1992; Slesinski et al., 1995; Lyle et al., 1998; Newman et al., 1998). This profile is similar to that for people using herbal supplements, with a few exceptions. Herbal use does not increase with age, and although those with health insurance are more likely to use vitamins or minerals, those without health insurance are more likely to use herbs (Fennell, 2004). Nationally representative data from NHANES indicate that although an increase in the use of supplements has occurred since the passage of DSHEA, usage patterns among various demographic groups are similar to those reported by researchers using nonrepresentative population samples.

Reasons cited for usage of dietary supplements by various subgroups suggest that a large segment of people living in the United States is adopting a health-promotion strategy that includes seeking alternative forms of medicine (Slesinski et al., 1995; Eliason et al., 1997; Eisenberg et al., 1998; Patterson et al., 1998; Gilbert, 1999; Hensrud et al., 1999; Radimer et al., 2000; Greger, 2001). Supplements are used to improve nutrition, make up for nutrients missing in the diet, decrease susceptibility to or severity of disease, increase energy (vitality), or improve performance. Herbal and botanical preparations are frequently used to supplement conventional medical treatments. Those most commonly used by the general population before 1995 were garlic and lecithin (Radimer et al., 2000). In 2003, the top-selling herbals were weight-loss blends with and without ephedra and glucosamine/chondroitin sulfate (*Nutrition Business Journal*, 2004). It is interesting that many dietary supplement users report that they do not discuss their supplement use with their physicians because they believe that physicians are biased against, and not knowledgeable enough about, supplements (Hensrud et al., 1999).

Dietary Supplement Use among People with Cancer

Given the prevalence and usage trends of dietary supplements in the general population, it is not surprising to see similar trends among people who have been diagnosed with cancer. However, the majority of prevalence studies do not collect data on supplement use before cancer diagnosis but only provide information on supplement use after diagnosis. This disallows inferences to be made on the role of a cancer diagnosis as a motivator for dietary supplement use. In general, motivators for supplement use among cancer patients include maintenance of health, increased well-being, prevention of recurrence, and alleviation of symptoms. Tables 1, 2, and 3 summarize studies published since 2000 that provide prevalence data on dietary supplement use among people with cancer. Table 1 summarizes studies with data from pools of cancer patients, generally adults. The range of any supplement use in this set of studies is between 29 and 80%. Multivitamins were the most frequently used supplement; vitamins A, B, C, and E were the most frequently used single vitamins; calcium and selenium were the most frequently used single minerals; garlic, ginseng, and soy were the most frequently used botanicals; and shark cartilage, hydrazine sulfate, and coenzyme Q10 (CoQ10) the most frequently used nonbotanical dietary supplements. However, the list of other supplements used by any proportion of the study samples is extensive. Table 2 focuses on studies with data from people with specific cancer diagnoses (in which the range of supplement use is between 35 and 64%), and Table 3 presents two studies published on pediatric cancer patients.

Among studies on the general adult cancer patient population, two compared dietary supplement usage by people with cancer to people not diagnosed with cancer. The first of these analyzed data from the NHIS in 1987 and 1992 (McDavid et al., 2001). Among both populations in this nationally representative survey, multivitamins were more commonly used than other supplements (taken by 75%), although ~50% of both groups reported taking vitamin C. It is important to note that this is not necessarily daily use, but any use during the period for which data were collected. Unfortunately, the small sample size of the cancer cohort (689 people) provided little power to test differences between this group and those not reporting a diagnosis of

TABLE 1 Prevalence of Dietary Supplement Use among People Diagnosed with Cancer

Reference	Type of study	Location	Population	N	Results
McDavid et al., 2001	Cross-sectional, nationally representative probability household survey	Entire United States	Male and female cancer survivors (median age 63 years) and individuals with no reported history of cancer (median age 40 years)	33,456 (689 cancer survivors and 32,767 without cancer)	Vitamin and mineral supplement use similar in both groups; >75% took multivitamins and almost half took vitamin C; among cancer survivors, calcium use was significantly higher among women (34.9%) than men (13.8%), and vitamin A use was higher among men (9.0%) than women (7.6%)
Metz et al., 2001	Prospective evaluation of consecutive patients at a university cancer center	Philadelphia, Pennsylvania	Patients with a malignancy at first visit; median age 61 years	196 (133 men and 63 women)	79 individuals reported use of "unconventional medical therapies"; among them, 46% took megavitamins (especially high-dose vitamin C [at >10 g/day] and vitamin E), 34% took herbal supplements (23 identified), and 16% took other supplements (such as shark cartilage and hydrazine sulfate); admitting use of unconventional therapies increased from 7% to 40% when patients directly queried
Kumar et al., 2002	Retrospective chart review of consecutive patients at a university cancer center	Tampa, Florida	Patients ranging in age from younger than 30 years (4% of total) to older than 60 years (56% of total)	237 (120 men and 117 women)	139 individuals took multivitamins/mineral supplements, 205 used individual vitamins (vitamins E and C most frequently), 104 used botanical supplements (typically garlic, ginseng, soy, ginkgo, and echinacea), and 67 used individual minerals (calcium, followed by iron and selenium)
Greenlee et al., 2004	Cross-sectional cohort study of participants in the Vitamins and Lifestyle (VITAL) study	Western Washington State	Men and women 50–76 years of age	75,083 (10,857 cancer survivors and 64,226 cancer-free controls)	Both groups took similar numbers of supplements. Among cancer survivors, 47.3% and 54.5% of men and women, respectively, took a multivitamin, 41.0% and 57.5% had high use (two or more per day) of vitamin and mineral supplements, and 16.0% and 20.7% had high use of herbal and specialty supplements; strongest positive associations were found for cranberry pills with bladder cancer, zinc with ovarian cancer, soy with prostate cancer, melatonin with cervical cancer, and vitamin D with thyroid cancer
Hedderson et al., 2004	Telephone survey of randomly selected cancer patients in state surveillance system	Washington State	Individuals 20–70 years of age diagnosed with breast, colon, or prostate cancer	356 (178 men and 178 women)	54.5% of men and 72.5% of women took any vitamin or mineral supplement beyond a basic multi; 32.6% of men and 42.7% of women took any herbal or other type of supplement; conclusion: men and women "differ considerably" in their use of complementary and alternative medicine, including use of dietary supplements
Jazieh et al., 2004	Cross-sectional study of cancer patients at a veterans' hospital oncology clinic	Cincinnati, Ohio	Military veterans with a malignancy; median age 68 years	200 (196 men and 4 women)	Most commonly used supplements were multivitamins (80.3%) and minerals (40.6%); 10 took herbal supplements. 74% of users reported benefits, including improved health and energy; 38% did not disclose supplement use to their physicians

TABLE 2 Prevalence of Dietary Supplement Use by Diagnosis of Breast, Prostate, and Colorectal Cancer

Reference	Type of study	Location	Population	N	Results
Lengacher et al., 2002	Descriptive cross-sectional survey	Tampa, Florida	Convenience sample of women with diagnosis of breast cancer; mean age 59 years	105	On regular basis, 64% used vitamin and mineral supplements, 33% took antioxidants, and 13% used herbs; more than half did not take supplements before diagnosis, and majority discussed supplement use with doctor
Hall et al., 2003	Descriptive survey of responses to mailed questionnaire	Charlottesville, Virginia	Men treated for prostate cancer at a medical center	238	84 took vitamins (53 used vitamin E), 52 took a multivitamin, and 29 used an herbal supplement (most commonly lycopene and saw palmetto); many believed supplements helped cure their cancer and helped them to feel better
Patterson et al., 2003	Telephone survey of randomly selected patients in state surveillance system	Washington State	Adults with breast, prostate, or colorectal cancer	356 (126 with breast cancer, 116 with colorectal cancer, and 114 with prostate cancer	48% took new supplements after diagnosis (primarily multivitamins, vitamins E and C, calcium, garlic, and echinacea); women were 2.2 times more likely to do this than men; >90% reported that supplement use improved health and well-being
Rock et al., 2004	Multisite, randomized controlled trial	Sites in California, Arizona, and Oregon	Women with history of early-stage breast cancer	3,008	At enrollment, 58% took multivitamins, 46% vitamin E (17% of them at intakes ≥500 mg/day), 42% vitamin C (24% at intakes ≥1000 mg/day), 11% vitamin A and carotenoids, and ~10% antioxidant mixtures; trend toward use of multi-ingredient products containing herbs; supplements commonly used for general health and "to feel better"
Salminen et al., 2004	Responses to questionnaires administered to patients on site	Melbourne, Australia and Turku, Finland	Women with newly diagnosed breast cancer	354 (215 from Australia and 139 from Finland)	50% of the Australians and 47% of the Finns took supplements, primarily vitamins and minerals

cancer. The second such study offering comparative statistics was the Vitamins and Lifestyle (VITAL) study, composed of a self-selected sample of adults in western Washington State, most of whom took at least one vitamin supplement at the start (Greenlee et al., 2004). This study, which focused on supplement use at least five times weekly, showed little difference among cancer patients and those without cancer with respect to both multivitamin, single vitamin or mineral supplement, and herbal supplement use. Differences among prevalence rates reported in these and the remaining four studies in Table 1 reflect variation in study design and outcome indicators (Metz et al., 2001; Kumar et al., 2002; Hedderson et al., 2004; Jazieh et al., 2004).

The differences in results reported in Table 2 also reflect the variation in study design, sample selection, and outcome variables. Patterson et al. (2003) only report on new supplements taken after a diagnosis of breast, prostate, and colorectal cancer and do not include usual supplements taken before and after diagnosis. Hall et al. (2003) limited their study to men with prostate cancer, and Lengacher et al. (2002) and Salminen et al. (2004) limited their studies to

TABLE 3 Prevalence of Dietary Supplement Use among Pediatric Cancer Patients

Reference	Type of study	Location	Population	N	Results
Neuhouser et al., 2001b	Telephone survey of parents of randomly selected patients in state surveillance system	Western Washington State	Pediatric cancer patients 18 years or younger	75	After cancer diagnosis, subjects took miscellaneous supplements (n = 28; including antioxidant mixtures and shark cartilage), herbal supplements (14), single-nutrient supplements (13), vitamin C (7), and echinacea (6); majority used supplements to maintain health or to treat noncancer symptoms like cold and flu
Ball et al., 2005	Convenience sample of parents of chronically ill patients who completed questionnaire at clinic	Salt Lake City, Utah	Children and adolescents with solid-tumor cancer or leukemia (mean age ~9 years)	100 (50 with each type of cancer)	50% took supplements (typically without doctor's knowledge), primarily vitamins, botanicals, and minerals; most common reasons: improve health, supplement diet, and prevent disease; supplements were discontinued within past year by one third of parents

women with breast cancer. Rock et al. (2004) presented comparative data from a study conducted with breast cancer patients and one with the general population. Reported multivitamin use in women with a history of early-stage breast cancer in the Women's Healthy Eating and Living (WHEL) Study (n = 3,088) was 58%, with 42% using vitamin C.

The two studies of children with cancer (Table 3) also use different outcome measures. Ball et al. (2005) reported on the prevalence of dietary supplement use separately for children with leukemia and solid tumors (42% and 50%, respectively, used vitamins; 10% and 16% used minerals; and 18% and 24% used botanicals). Neuhouser et al. (2001b) did not differentiate by type of cancer and reported 29% use of single vitamin supplements, 15% use of vitamin and mineral mixtures, and 35% use of herbal supplements. Most parents of the children in this study reported perceived improvement from single vitamin use (76.9%) and herbal supplement use (85.7%). Motivators for dietary supplement use included treating side effects or symptoms of cancer or cancer treatment (47.2%), preventing recurrence or spread of cancer (33.3%), preventing or treating noncancer symptoms such as a cold or flu (51.4%), and maintaining general good health (72.2%).

Despite the variations in populations, study design, sample size, and outcome variables, it is clear that significant proportions of people who have been diagnosed with cancer are using dietary supplements. This underscores the need for additional information on the efficacy and safety of these supplements for people with different types of cancers, undergoing different types of treatments, and at varying stages of life.

Importance of Evidence-Based Research

Any recommendations for supplementation must be based on scientific evidence that the supplements are both effective and safe. Ideally, a rigorous systematic research approach (Table 4) is carried out and the results are evaluated to assess the health benefits of a dietary supplement and whether its use is recommended. The review begins with preclinical (*in vitro* and *in vivo* studies) and epidemiological evidence. Although these lines of evidence may provide insight into anticipated outcomes, it is important that research be taken to the next level of clinical trials. Before the conduct of human clinical trials, however, all available evidence must be reviewed thoroughly and objectively to determine whether data on efficacy and safety justify proceeding to clinical trials. Such evidence-based reviews differ from traditional opinion-based narrative reviews in that they systematically attempt to reduce bias by the comprehensiveness and reproducibility of the search for and selection of articles for review. Systematic reviews also assess the methodological quality of the included studies and evaluate the overall strength of the body of evidence (Agency for Healthcare Research and Quality [AHRQ], 2002). When the body of evidence on safety and efficacy justifies proceeding to clinical trials, the trials are usually conducted in three

TABLE 4 Evaluating Dietary Supplements: A Research Approach

BASIC BIOMEDICAL LABORATORY RESEARCH
(*In vitro* experiments and *in vivo* animal experiments)
↓
HUMAN OBSERVATIONAL EPIDEMIOLOGICAL STUDIES
(Identify possible links between dietary supplements and cancer prevention)
↓
HYPOTHESIS DEVELOPMENT
(Evaluation of existing laboratory and epidemiological evidence on dietary supplement safety and effectiveness: as related to cancer prevention and therapy)
↓
DECISION POINT → DO NOT PROCEED
↓
PROCEED
↓
HUMAN SAFETY TRIALS
(Identify adverse side effects: safe dosage: and potential interactions)
↓
SMALL TRIALS IN DEFINED POPULATIONS
(Measure supplement effectiveness at various safe doses)
↓
LARGE-SCALE: DOUBLE-BLIND: PLACEBO-CONTROLLED: RANDOMIZED CLINICAL INTERVENTION TRIALS
(Test whether supplementation has the hypothesized human health benefit)
↓
DEVELOP SUPPLEMENTATION RECOMMENDATION

phases: human safety trials, small efficacy trials (usually in defined target groups), and large-scale trials that are essential in moving from basic and observational science to evidence-based public health recommendations that have human benefits.

The large-scale, double-blind, randomized, placebo-controlled clinical trial, which is designed to eliminate all possible bias, is considered the gold standard of scientific intervention research. In such trials, some people receive the substance being tested and some receive an inactive placebo. These trials may not be possible in all circumstances, however, because of ethical issues that make it inappropriate to withhold the substance being tested from any trial participants. For example, after it was observed that low folate intake by pregnant women was linked to neural tube defects, a placebo-controlled intervention trial to test the validity of this association would not have been ethical. In such cases, all available evidence from *in vitro* laboratory research and *in vivo* animal studies, as well as epidemiological studies and surveys, must be reviewed systematically and objectively to draw conclusions about the possible effectiveness and safety of the supplement of interest and to make recommendations for supplementation.

Two evidence-based reviews have been conducted on the effect of specific supplements on cancer prevention. The first was a review by the U.S. Preventive Services Task Force (PSTF) on routine vitamin supplementation to prevent cancer and cardiovascular disease. For cancer, the PSTF recommended against the use of β-carotene supplements, either alone or in combination, and concluded that insufficient evidence exists either for or against the use of supplements of vitamins A, C, or E, multivitamins with folic acid, or antioxidant combinations for the prevention of cancer (PSTF, 2003). The second systematic review by the AHRQ on the use of the antioxidant vitamins C and E and CoQ10 supported the PSTF recommendations for vitamins C and E and determined that the literature does not support the use of CoQ10 supplements to help prevent or treat cancer (AHRQ, 2003). The AHRQ recognized that a few individual trials did report benefits in patients with bladder cancer and that other trials reported beneficial intermediate outcomes, such as colonic crypt cell proliferation with vitamin C and E supplementation.

Although clinical trials provide a wealth of information, various interactions must be accounted for when interpreting the results and developing public health recommendations. These factors include a person's stage of life, general health status, genetic makeup, and health and lifestyle behaviors. Each may influence the absorption, usefulness, and need for any particular dietary supplement. For example, the results of a large randomized clinical trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study conducted in Finland suggested a substantial benefit of vitamin E in reducing prostate cancer (Heinonen et al., 1998). However, almost all the participants were current or past smokers.

Another major concern associated with clinical trials designed to evaluate the health effects of dietary supplements is that participants might take additional supplements, which could influence trial outcomes. In the Prostate Cancer Prevention Trial (PCPT) of the drug finasteride, for example, almost half of the participants reported using a multivitamin supplement, about a third used single supplements of either vitamin C or E, and one in five used calcium supplements. Limitations to the study included the lack of control for dosage amount, frequency of intake, type of supplement, and the limited data on micronutrient intake from fortified foods (Neuhouser et al., 2001a). Very little evidence is available about how individual micronutrients might interact with one another to influence health outcomes. The Selenium and Vitamin E Prevention Trial (SELECT) is expected to help clarify the association of dietary supplement use with prostate and other cancers. SELECT is a randomized, prospective, double-blind study designed to determine whether selenium and vitamin E reduce the risk of prostate

cancer in healthy men (Klein et al., 2003). The vitamin E supplement will be a higher dose than that used in the ATBC study (400 vs 50 mg), and final results are expected in 2013.

The following section explores the relationship of these interactive factors with respect to the role of dietary supplements and cancer.

ROLE OF DIETARY SUPPLEMENTS IN CANCER PREVENTION AND DURING THERAPY

To understand the potential role of dietary supplements in the prevention of cancer, scientists have developed models of molecular mechanisms through which nutrient and nonnutrient supplements might affect metabolic processes that lead to cancer. Potential mechanisms include inhibiting carcinogen uptake, inhibiting the formation or activation of carcinogens, and preventing dietary carcinogen binding to DNA (American Institute for Cancer Research, 2000). Different supplements use different pathways to influence carcinogenesis. For example, antioxidants neutralize free radicals, preventing them from damaging other molecules, which over time may lead to cancer. In addition to the well-known antioxidants (vitamin C, vitamin E, and β-carotene), other substances such as mistletoe extract exhibit antioxidant properties. Calcium inhibits carcinogen uptake most often in conjunction with vitamin D. Folic acid helps to synthesize and repair DNA, potentially preventing cancer development. Phytoestrogens, the most common of which (genistein and daidzein) come from soy products, may inhibit the growth of estrogen receptor (ER)-positive and ER-negative breast cancer cells (Jennings, 1995; Peterson and Barnes, 1996). These are only a few supplement-related mechanisms that have been or are being studied.

Researchers have also investigated additional factors that might influence the involvement of dietary supplements in the prevention of cancer. They include the timing of supplement use, the effect of dose and dose–response, the role of specific supplement components, and the impact of interactive factors. Each factor is discussed in the following subsections with examples.

Timing

The issue of timing in dietary supplement use with respect to cancer prevention and treatment reflects on the age of the person and the time within the course of the disease that supplements are taken. A better understanding of these issues may help explain some of the conflicting results from epidemiological and clinical studies on dietary supplement use. Calcium and the soy isoflavone genistein provide examples of the importance of timing in supplement use.

Timing with the Framework of a Day: The Example of Calcium

Calcium has been investigated for its role in cancer prevention because it participates in multiple molecular signaling pathways and alterations of gene expression associated with cancer and for its role in many other key biological processes, such as bone formation and proper functioning of the nervous system (NIH Consensus Conference, 1994; Patton et al., 2003). However, the time of supplementation may influence its impact. Ingesting calcium supplements between meals supports calcium bioavailability because some foods contain compounds such as oxalates that reduce calcium absorption (NIH Consensus Conference, 1994). Also, high intakes of calcium from foods or supplements taken with meals may inhibit nonheme iron absorption and negatively affect the redox and antioxidant availability of iron (NIH Consensus Conference, 1994; Whiting, 1995).

Timing with the Lifespan: The Example of Phytoestrogens

Another example of timing is exposure during different periods of life. Throughout the lifespan, estrogens increase mammary cell proliferation, but other factors, such as hormonal levels, may influence estrogens' ability to induce differentiation or affect mammary growth by other means. Thus, estrogens can have a different impact on the breast if the exposure occurs *in utero*; during childhood, puberty, or pregnancy; premenopausally; or during postmenopause (Hilakivi-Clarke and Clarke, 1998). There is evidence that genistein also has different effects on the breast depending on the timing of exposure. For example, studies in rats have shown that prepubertal exposure to genistein protects against chemically induced mammary tumors, possibly because genistein increases cellular differentiation at early stages of mammary development (Lamartiniere et al., 2002). During the reproductive years, genistein increases mammary gland proliferation, as has been shown in both animal and human studies (Petrakis et al., 1996; Hsieh et al., 1998; McMichael-Phillips et al., 1998). Differences have been noted in the effect of genistein premenopausally and postmenopausally. Although there is no evidence that genistein promotes breast cancer in premenopausal women, animal studies suggest that it may play a role in the growth of cancer cells in postmenopausal women (Hsieh et al., 1998; Trock et al., 2000). It is possible that the different impact of genistein on premenopausal and postmenopausal women reflects the increased likelihood that postmenopausal women already have malignant cells in their breasts and that genistein, acting as an estrogenic agent, proliferates mammary cell growth, be it healthy or malignant cells (Bouker and Hilakivi-Clarke, 2000).

Dose and Dose–Response

Because dietary supplements are ingested to add to or replace dietary factors generally found in food products, issues of dose and bioavailability are important in discussions of their efficacy and safety. Often, the dose of a dietary supplement is greater than the amount normally found in food and may equal or exceed recommended levels of intake. For example, the recommendation for vitamin C is 75 mg/day for adults older than 18 years, but an average dose of a vitamin C supplement is 500 mg. Although dietary recommendations suggest the value of eating large amounts of fruits and vegetables, which contain vitamin C and other antioxidants, research is necessary to determine the levels of specific nutrient or nonnutrient components of these foods, which when used as supplements will have an impact on carcinogenesis.

Vitamin A and β-Carotene

For example, both the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study and the β-Carotene and Retinol Efficacy Trial (CARET) reported that the use of β-carotene supplements in smokers may promote lung cancer (ATBC Study Group, 1994; Omenn et al., 1996). Among the explanations for these results is that the dose of β-carotene in the trial was 5–10 times greater than that supplied by a healthy diet; this higher dose may have inhibited the absorption of other antioxidants with cancer-preventive properties (Greenwald, 2003). In addition, tissues of trial participants supplemented with β-carotene showed a 50-fold higher concentration than those of individuals who consumed large amounts of fruits and vegetables (Borrás et al., 2003).

Dose–response to vitamin A also is dependent on the vitamin A status of cells. Vitamin A circulates in the body after binding to a retinol-binding protein (RBP), which is accumulated in the liver, and homeostasis results in extra retinol being stored for future use. When cells are deficient in vitamin A, the liver accumulates large amounts of RBP in anticipation of future availability of the vitamin (Russell, 2000). Ingesting vitamin A through the diet or by supplement in a vitamin A–deficient state causes a rapid large rise in serum retinol that is short-lived. Vitamin A ingestion when cells are not deficient results in a slower and smaller rise in serum retinol, with extra amounts being stored for later use (Russell, 2000).

Vitamin E and Its Constituents

The two subgroups of vitamin E are tocopherols and tocotrienols. Tocotrienols have been shown to have potent anticancer activity at doses that do not appear to affect normal cell growth or function. Their antitumor activity is independent of antioxidant activity. Dose–response studies show that growth-inhibitory doses of tocotrienols are five to six times lower than their corresponding lethal doses, suggesting that different mechanisms control their antiproliferative and cytotoxic effects (Sylvester and Shah, 2005).

Folic Acid

Epidemiological studies suggest that dose and dose–response are important factors in folate supplementation to reduce cancer risk, especially for colon cancer and colorectal adenoma. A 35–40% risk reduction was observed in those with the highest folate intake compared with those with the lowest intake (Kim, 1999). A randomized study of patients with recurrent polyps reported that supplementation with 2 mg of folate significantly decreased colonic mucosal-cell proliferation in the treatment group compared with controls (no supplementation) (Khosraviani et al., 2002).

Calcium and Vitamin D

Calcium, which has the potential to reduce the risk of colon cancer, also has been shown to exhibit a dose–response relationship (Wu et al., 2002). Data from the Nurses' Health Study (Martínez et al., 1996) and Health Professionals Follow-up Study (Kearney et al., 1996) indicate that higher calcium intake is associated with a reduced risk of distal colon cancer. The incremental benefit of additional calcium intake >700 mg/day was minimal. Interestingly, it has been shown that the relationship between calcium and vitamin D is important in their associations with cancer risk (Milner et al., 2001). Results of the Calcium Polyp Prevention Study show that vitamin D status strongly influenced the impact of calcium supplementation on adenoma recurrence (Grau et al., 2003). Calcium supplements only lowered the risk of adenoma in subjects with 25-hydroxyvitamin D levels above the median. Similarly, 25-hydroxyvitamin D was associated with reduced risk only among those supplemented with calcium. It was concluded that vitamin D and calcium supplements appear to act together, not separately, on colorectal carcinogenesis.

Interactive Impacts: Environment, Gender, Genetic Differences

Environmental, genetic, and other differences may determine whether benefit or harm is derived from the use of dietary supplements in healthy individuals, populations at risk for certain diseases, and patients undergoing disease therapy. Selenium, folate, genistein, and zinc are examples of dietary supplements that have been investigated for their association with environmental, genetic, and hormonal factors and cancer risk.

Environmental Factors

Epidemiological studies suggest an increase in colon cancer in areas where selenium levels are low in the soil (Clark et al., 1991). Because the amount of selenium provided by the diet is dependent on the amount found in the soil used to grow food products, the level of intake among populations is varied, especially when most food consumed comes from a single geographic source. Clinical trial results from Linxian, China, an area characterized by epidemic rates of squamous esophageal and adenomatous gastric-cardia cancers, indicated a significant inverse association of serum selenium levels with these cancers when the highest-to-lowest quartiles of serum selenium were compared (Mark et al., 2000). Selenium supplementation has been associated with a reduction in prostate, lung, and colorectal cancers (Greenwald et al., 2002).

Genetic Factors

Genetic variability and selenium intake may both play important roles in reducing cancer risk. A large randomized phase III trial, The Selenium and Vitamin E Cancer Prevention Trial (SELECT), is investigating the effect of supplementation with selenium and vitamin E, alone or in combination, on prostate cancer incidence. A nested case-control study within SELECT will assess genetic polymorphisms of four genes (androgen receptor [*AR*], 5α-reductase type II [*SRD5A2*], cytochrome P450c 17α [*CYP17*], and β-hydroxysteroid dehydrogenase [*HSD3β2*]) on prostate cancer incidence (Hoque et al., 2001). *CYP17* is of particular interest because previous studies have suggested that the A1/A1 genotype confers a significantly higher serum androgen level than is found in men with either the A1/A2 or the A2/A2 genotype.

Folate provides another example of genetic differences that can influence the potential benefits of supplementation. Methylenetetrahydrofolate reductase (MTHFR) is a critical enzyme that regulates the metabolism of folate by converting 5,10-methylenetetrahydrofolate (methyleneTHF) to 5-methyltetrahydrofolate (methylTHF), the major form of circulating folate in plasma. A common polymorphism of the *MTHFR* gene (677C→T) results in an alanine→valine substitution in the enzyme and, subsequently, in significantly decreased activity (Greenwald et al., 2002). This results in increased methyleneTHF, which results in reduced incorporation of uracil in DNA, which leads to fewer chromosome breaks and possibly reduced cancer risk (Greenwald et al., 2001).

Studies of data from the Health Professionals Follow-Up Study and the Physician's Health Study on the 677→6T *MTHFR* polymorphism and dietary intake of folate in colorectal tumorigenesis found that when the dietary methyl supply was high, individuals with the *MTHFR* polymorphism were at reduced risk of colorectal cancer. Interestingly, alcohol consumption reversed this association—possibly by depletion of the dietary methyl supply and folate breakdown by acetaldehyde—and suggests that individuals with this genotype may be more susceptible to the carcinogenic effects of alcohol (Greenwald et al., 2001).

Epidemiological studies report that zinc deficiency is associated with an increased risk of esophageal squamous cell carcinoma in high incidence areas of China and Iran (Fong et al., 2003). Abnormalities in the *p53* tumor suppressor gene, which causes a loss of function leading to increased tumor proliferation and decreased apoptosis, has been studied in zinc-deficient mice exposed to the carcinogen N-nitromethylbenzylamine (NMBA). An investigation of esophageal NMBA-induced tumor proliferation in *p53–/–* zinc-deficient mice suggests that zinc modulates genetic susceptibility to cancer caused by *p53* inactivation (Fong et al., 2003).

Hormonal Factors

The relationship between genistein and hormones in the lifespan of women was described in the section "Timing with the Lifespan: The Example of Phytoestrogens." In men, epidemiological and experimental evidence suggests that genistein may inhibit prostate tumor growth through various mechanisms, including cell proliferation and increased apoptosis (Greenwald et al., 2002). In a study in LNCaP prostate cancer cells, genistein completely inhibited expression of prostate-regulated transcript 1 (*PART-1*), an androgen-induced gene that may represent a novel tumor marker for prostate cancer (Yu et al., 2003). In a small study of patients with prostate cancer, a dietary supplement of red-clover isoflavones, including genistein, was administered before surgery. After prostatectomy, apoptosis in cells from treated patients was significantly higher than in cells from controls, specifically in regions of low- to moderate-grade cancer (Jarred et al., 2002).

Therapeutic Interactions

Just as there are many mechanisms through which dietary supplements influence the prevention of cancer, so are there a variety of ways in which they influence cancer treatment. The following highlights some of the mechanisms that have an impact on the efficacy of treatment and its side effects. This is not meant to be a complete list of all influential factors, but a highlight of examples of potential interactions.

Antioxidants

Chemotherapeutic agents include alkylating agents (cyclophosphamides), anthracycline antibiotics (doxoru-

bicin), platinum compounds (cisplatin), mitotic inhibitors (vincristine), antimetabolites (5-fluorouracil), camptothecin derivatives (topotecan), biological response modifiers (interferon), and hormonal therapies (tamoxifen). Anticancer therapies that may potentially be influenced by antioxidants include: alkylating agents (cyclophosphamide and iphosphamide), platinum compounds (cisplatin), antibiotics (doxorubicin and bleomycin), topoisomerase II inhibitors (etoposide), and radiation (Conklin, 2000). However, the evidence with respect to the impact of antioxidants on chemotherapy or radiation is controversial. Studies show both that antioxidants are safe and effective enhancers of chemotherapy and that they interfere with the oxidative breakdown of cellular DNA and cell membranes needed for the chemotherapy to be effective (Norman et al., 2003). Although most clinical trials have not shown significant impacts of antioxidant supplementation on chemotherapy or radiation, some have reported either the potentiation or the inhibition of these therapies by antioxidants (Weiger et al., 2002). Three clinical trials indicate that melatonin (an antioxidant) enhances the efficacy of radiation therapy and chemotherapy (Lissoni et al., 1996, 1997, 1999). Animal studies indicate that the impact of antioxidants may depend on dosage and timing of administration with respect to radiation (Sakamoto and Sakka, 1973).

Phytoestrogens

As was discussed in the section "Timing with the Lifespan: The Example of Phytoestrogens," soy isoflavonoids, particularly genistein and daidzein, have both positive and negative estrogenic effects on breast tissue. In a review of 26 animal studies, soy was found to have a positive effect in most cases (Messina et al., 1994). However, other animal studies suggest the need for concern that soy supplementation in women with breast cancer, particularly with ER-positive tumors, may cause a proliferation of the cancerous cells (Weiger et al., 2002). A review addressed this dichotomous role and concluded that the data are not strong enough on either side to support the use or nonuse of soy supplements (Messina and Loprinzi, 2001). Additional effects of soy on cancer treatments have also been examined. Animal study data indicate that genistein can negate the inhibitory effect of tamoxifen on breast cancer growth (Ju et al., 2002). Given its antioxidant activity, there is also concern with respect to the use of soy supplementation during radiation or chemotherapy (Wiseman, 1996).

Other Supplements

Supplements that are neither antioxidants nor phytoestrogens also may affect treatment. Blood levels of medications may be influenced by the use of St. John's wort. This herb is an inducer of the cytochrome P450 enzyme system and drug-transporting P glycoprotein. Studies have found that St. John's wort reduces levels of drugs such as cyclosporine and indinavir, as well as levels of the active metabolite of irinotecan, a chemotherapeutic agent (Mathijssen et al., 2002; Weiger et al., 2002).

CONCLUSIONS

Despite varied results with respect to specific foods and specific cancers, results of observational, ecological, and clinical studies provide strong evidence that diets high in vegetables, fruits, and plant-based foods and low in animal fats lower the risk for cancer. The specific agents responsible for cancer protection are unknown (World Cancer Research Fund, 1997). At best, the evidence is mixed that dietary supplements taken for health promotion and disease prevention actually provide the benefits expected by consumers and patients. However, given the high rate of dietary supplement use among the general population and those diagnosed with cancer, a better understanding of possible differences between a dietary factor in food and the same factor as a supplement is necessary. As new molecular and technological approaches are developed to study the nutritional sciences, investigations can be designed to elucidate the mechanisms of action of dietary factors in both forms. Experimental and animal models must be developed to help assess the safety and efficacy of the multitude of vitamins, minerals, and botanicals in the marketplace. Also, identification and use of intermediate outcomes as endpoints in future clinical research could provide a more cost-effective method for gauging the efficacy of dietary supplements. Furthermore, attention should be directed toward possible confounding effects of supplement use by participants in clinical trials for cancer prevention and control. From a broader research perspective, there is a need to investigate dietary supplement use in the context of health disparities and cultural, ethnic, and demographic determinants. A better understanding of supplement timing, dose and dose–response, and vulnerability of specific populations is essential for providing scientifically sound information on the use of dietary supplements.

Important issues to be addressed in research aimed at determining the effects of dietary supplements on cancer include developing better methods to measure the contribution of dietary supplements for various population groups and to monitor these usage trends over time. Although data are available on the prevalence of dietary supplement use among people with cancer, the data collection is not systematic and the data are not collected both before and after cancer diagnosis. The majority of information is collected on people who have been diagnosed with cancer. This makes inferences to the role of supplements in cancer prevention difficult, if not impossible. Although some of the nationally representative survey data provide comparisons between

cancer patients and individuals not diagnosed with cancer, the number of cancer patients is too small, limiting the strength of the comparative results. Additionally, although some studies collect data on new supplement use (post diagnosis), most do not ask about length of time for which supplements have been used.

The systematic collection of prevalence data could include the development of a set of core prevalence indicators that include definitions of *cancer patient* or *survivor*, frequency of supplement use (daily, regularly, ever), length of time a supplement has been used, supplement dose (low to high for each supplement), motivators for use, perceived benefits, and other user characteristics. Such systematic prevalence data could assist researchers, healthcare professionals, and policymakers in identifying the supplements most frequently used and the characteristics of those most likely to use them, helping to set an agenda for future research. Along with ensuring that prevalence data on supplements includes botanicals and other nonbotanical nonmicronutrient products, additional work is necessary to understand how best to ask people questions about these supplements, given the different languages and names used in their sale, the multitude of herbal combinations used, and the variety of forms in which people take them (e.g., prepared teas, concentrated drinks, powders, and tablets).

Taking dietary supplements is likely to remain a significant strategy used by consumers and patients to improve health and combat diseases such as cancer. The scientific community must respond by providing guidance about the responsible use of these products to the public, medical professionals, and policymakers that is based on sound scientific evidence. Research—experimental, epidemiological, and clinical—on nutrition and cancer is the best way to identify dietary factors that show promise as cancer prevention or control agents. This approach will allow scientists to either confirm or refute the growing amount of consumer information on the benefits and risks of dietary supplement use. Physicians and healthcare providers need to openly discuss the use of dietary supplements with their patients, especially because many supplement users get most of their information about these products from friends, family, the media, and other word-of-mouth sources. Patients need to understand the potential positive and negative impacts of the supplements they may choose to use and need to be informed that supplements should not be used as a substitute for medical therapies. Healthcare providers should encourage patients to enumerate the various supplements they take and provide expert advice about using these products responsibly. The NIH Office of Dietary Supplements, for example, provides helpful materials for this purpose, including a consumer-friendly brochure titled "What Dietary Supplements Are You Taking? Does Your Health Care Provider Know? It Matters and Here's Why" (Office of Dietary Supplements, 2005).

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