Natural Products for Cancer Prevention

Heather Greenlee

Objectives: *To review the clinical trial literature on the use and effects of natural products for cancer prevention.*

Data Sources: *Clinical trials published in PubMed.*

Conclusion: *There is a growing body of literature on the use of natural products for cancer prevention. To date, few trials have demonstrated conclusive benefit. Current guidelines recommend against the use of natural products for cancer prevention.*

Implications for Nursing Practice: *Clinicians should ask patients about their use of natural products and motivations for use. If patients are using natural products for cancer prevention, they should be counseled on the current guidelines, as well as their options for other cancer prevention strategies.*

Key Words: *Cancer, cancer prevention, multivitamins, vitamins, botanicals, medicinal mushrooms, probiotics*

INDIVIDUALS born in the United States today have a 41% lifetime risk of being diagnosed with cancer, a sobering statistic that has urged the health care community to identify effective methods of cancer prevention.[1] Primary cancer prevention aims to reduce the risk of an individual developing cancer through the use of chemopreventive agents, the avoidance of exposure to environmental carcinogens, and the surgical removal of susceptible organs.[2] Secondary cancer prevention relies on early detection and screening measures to identify precancerous and/or early stage tumors that are often more responsive to treatment than later stage tumors. Tertiary cancer prevention, often referred to as *cancer control*, aims to reduce the risk of recurrence, reduce the risk of metastasis, prevent second primary cancers, and prevent other cancer-related complications. This article focuses on the use of natural products for primary cancer prevention. The article reviews the clinical trial evidence on the effectiveness of natural products for cancer prevention, including vitamins and minerals, botanicals, probiotics, and other agents of interest.

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The use of natural products has increased in the United States. In 2007, approximately 18% of American adults reported using natural products beyond a basic multivitamin.[3] Individuals use natural products for a variety of health reasons, including treating and preventing disease, maintaining health, and promoting wellness. The evidence for this use is mixed and individuals do not use natural products in isolation. Many people use multiple natural products simultaneously and also engage in other health-related behaviors, such as dietary changes, physical activity, and the use of medications to prevent and treat disease. Factors associated with the use of natural products include prior use of natural products, higher age, higher education, and higher income.[4] There is a common perception that natural products are safe because they are "natural," but a natural product is not necessarily a safe product.[5]

Natural products are of particular interest as chemopreventive agents because of their potentially low toxicity profiles and potential effectiveness.[6] The National Center for Complementary and Alternative Medicine defines natural products as dietary supplements and include vitamins, minerals, probiotics, and herbal medicines.[3] The National Cancer Institute's Office for Cancer Complementary and Alternative Medicine (OCCAM) uses slightly different terminology for dietary supplements used as chemopreventive agents, referring to them as nutritional therapeutics, which include an assortment of nutrients, non-nutrients, and bioactive food components.[7]

The efficacy of natural products as chemopreventive agents for primary and tertiary cancer prevention has not yet been established. Observational studies have suggested that various vitamins, minerals, and dietary components reduce the risk of developing specific cancers. However, clinical trials have not always supported these observations and/or the trials have not been conducted to test the efficacy of the natural products as chemopreventive agents. Current guidelines from the American Institute of Cancer Research, the American Cancer Society, and the Society for Integrative Oncology recommend against the use of dietary supplements for cancer prevention based on the current evidence.[8-11] Many patients are not aware of these guidelines, or disregard the guidelines and use natural products with the intention of cancer prevention based on reports in the popular press and/or preliminary evidence.

Health care providers face many challenges when counseling patients on the use of natural products for cancer prevention. First, patients underreport use to their health care providers.[12] Reasons for this may include perceiving a lack of support for their use or fear of stigma from providers. Second, many health care providers believe that they are not qualified or sufficiently knowledgeable to counsel patients on the use of natural products.[13] Third, quality assurance of natural products is important.[14] Because the natural product industry is not tightly regulated by the US Food and Drug Administration, it can be challenging for health care providers to know whether a specific natural product is of high quality or not. Fourth, the evidence does not exist regarding the appropriate formulation, dose, duration, and cancer type for natural products.

This review provides an overview of commonly used natural products for cancer prevention, including a summary of the clinical trial literature to date. It is important to note that many of the results presented are based on post-hoc analyses, and are not the primary study outcomes, which may limit the generalizability and accuracy of the findings.

Summary of Research To Date

Vitamins and Minerals

Clinical trials examining vitamins and minerals as chemopreventive agents are summarized in Table 1.

Multivitamins and combinations. Multivitamins and combination vitamins are dietary supplements comprised of two or more single agents. They are commonly used to both improve the nutritional status among nutrient-deficient populations and to hyper-supplement nutrient-replete populations. The results of clinical trials examining the effects of multivitamins as chemoprevention agents remain mixed.

Intervention trials in Linxian, China showed the importance of multivitamin supplementation in nutrition-deficient populations to reduce the risk of esophageal, stomach, and other cancers.[15] The benefit of supplementation in nutrient-replete populations is not as clear. The Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) Trial showed that multivitamin use by

TABLE 1.
Clinical Trials Examining Vitamins and Minerals as Chemoprevention Agents

First Author, Study Name*	Population (Country)	Intervention	End Point	Results
Multivitamins and combinations				
Blot 1993[15] Nutrition Intervention Trial n = 29,584 Duration: 5.25 years	Healthy individuals ages 40-69 with no history of esophageal or stomach cancer (China)	Four combinations were tested. Participants were randomized to receive either all four combinations, two of the four combinations, or placebo. Doses of each nutrient ranged from one to two times RDA.	Cancer incidence (esophageal, gastric cardia, stomach, and other cancers), cancer mortality, and total mortality.	Those receiving beta carotene, vitamin E, and selenium experienced a significant reduction in overall mortality (RR=0.91; 95% CI=0.84-0.99), total cancer incidence (RR=0.87; 95% CI= 0.75-1.00), and stomach cancer incidence (RR=0.79; 95% CI=0.64-0.99).
Meyer 2005[16] SU.VI.MAX Trial n = 5,141 Duration: 8 years	Healthy men ages 45-60 (Canada)	Randomized, double-blind placebo-controlled trial. Participants received either placebo or a capsule containing vitamin C, alpha-tocopherol, beta-carotene, selenium, and zinc every day for 8 years.	Prostate cancer incidence	Among men with normal PSA levels, the rate of prostate cancer was significantly lower in those who received supplementation, (HR = 0.52; 95% CI = 0.29-0.92).
Vitamin C				
Moertel 1985[19] n = 100 Duration: Mean 2.5 months treatment for vitamin C and mean 3.6 months with placebo	Men and women with advanced colorectal cancer (United States)	Participants received either 10g of vitamin C or placebo daily	Progression of advanced colorectal cancer and survival	Vitamin C supplementation did not result in any significant difference in disease progression or survival.
Gaziano 2009[20] The Physician's Health Study II n = 14,641 Duration: 8 years	Male physicians aged 50 years or older (United States)	Randomized, double-blind, placebo-controlled factorial trial. Participants randomized to receive either: 1) vitamin E every other day and of vitamin C daily; 2) vitamin E every other day and placebo vitamin C daily; 3) placebo vitamin E every other day and vitamin C placebo daily; or 4) placebo vitamin E and C.	Total prostate cancer and total cancer for vitamin E component; total cancer, and incident colorectal cancer for vitamin C component; and total mortality and cancer mortality for both vitamin E and vitamin C.	Vitamin E did not significantly affect the incidence of prostate cancer or total cancer. There was no significant effect of vitamin C supplementation on total cancer incidence or prostate cancer incidence
Vitamin E				
Lonn 2005[24] Heart Outcomes Prevention Evaluation	Men and women at least 55 years old with vascular disease or	Randomized placebo-controlled trial. Participants	Cancer incidence and cancer mortality	There were no significant differences in incident cancers

(*Continued*)

TABLE 1.
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First Author, Study Name*	Population (Country)	Intervention	End Point	Results
(HOPE); HOPE - The Ongoing Outcomes (HOPE-TOO) n = 9, 541 for HOPE n = 7,030 for HOPE-TOO Duration: 7 years	diabetes mellitus (International)	randomized to receive 400 IU/day of vitamin E or placebo.		between the vitamin E group and the placebo group or in cancer mortality
Lee 2005[25] The Women's Health Study n = 39,867 Duration: 10.1 years	Healthy women aged 45 years or older (United States)	Randomized placebo-controlled trial. Participants were given either 600 IU of vitamin E or placebo on alternate days.	Total invasive cancer incidence; breast, lung and colon cancer incidence; cancer mortality	There were no significant differences between the two groups on the incidences of total cancer, breast cancer, lung cancer, or colon cancers. Vitamin E supplementation had no significant effect on cancer mortality
Lipmann 2009[21] Selenium and Vitamin E Cancer Prevention Trial (SELECT) n = 35,533 Duration: 5.5 years	Healthy men age 55 and older (age 50 and older if African American) with normal digital rectal exams and PSA levels <4 ng/ml (United States, Canada, Puerto Rico)	Randomized, placebo-controlled trial. Participants were randomized into four groups: 1) selenium, 2) vitamin E, 3) vitamin E and selenium, or 4) placebo.	Prostate cancer incidence, lung, colorectal, and overall primary cancer	Supplementation with vitamin E and/or selenium did not result in any significant differences in the incidence of prostate cancer
Klein 2011[23] Selenium and Vitamin E Cancer Prevention Trial (SELECT) n = 35,533 Duration: 7 years	Healthy men age 55 and older (age 50 and older if African American) with normal digital rectal exams and PSA levels <4 ng/ml (United States, Canada, Puerto Rico)	Randomized, placebo-controlled trial. Participants were randomized into four groups: 1) selenium, 2) vitamin E, 3) vitamin E and selenium or 4) placebo.	Prostate cancer incidence	Supplementation with vitamin E resulted in an increased of risk prostate cancer (HR: 1.17; 99% CI: 1.004-1.36, P=.008).
Selenium				
Yu 1991[26] n = 2,474 Duration: 2 years	Male and female first-degree relatives of liver cancer patients (China)	Participants were randomized to receive 200 μg selenium or placebo daily.	Liver cancer incidence	Liver cancer was lower in the selenium group although the results did not reach statistical significance.
Yu 1997[27] n = 226 Duration: 8 years	Male and female HBsAg carriers between the ages of 21 and 63 years (China)	Participants either were randomized to receive 200 μg of selenium or placebo for 4 years.	Liver cancer incidence	Liver cancer was lower in the selenium group although the results did not reach statistical significance.
Clark 1996[30] Nutritional Prevention Cancer Trial (NPCT) n = 1,312 Duration: 6.5 years	Men and women 18-80 years of age with a history of basal cell or squamous cell skin	A multicenter, double-blind, randomized, placebo-controlled trial. Participants were randomized to receive	Incidence of basal and squamous cell carcinomas of the skin, prostate, lung, and colorectal cancer.	Selenium treatment did affect the incidence of basal cell or squamous cell skin cancer: Patients

(*Continued*)

TABLE 1.
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First Author, Study Name*	Population (Country)	Intervention	End Point	Results
	carcinomas (United States)	200μg of selenium or placebo	All-cause mortality, total cancer mortality, and total cancer incidence.	treated with selenium had a significant reductions in total cancer mortality, cancer incidence and incidences of lung, colorectal, and prostate. Trial was stopped early because of the reductions in total cancer mortality and cancer incidence in the group
Clark 1998[31] Nutritional Prevention Cancer Trial (NPCT) n = 974 Duration: 6.5 years	Men with a history of either a basal cell or squamous cell carcinoma (United States).	A multicenter, double-blind, randomized, placebo-controlled trial. Participants were randomized to receive 200μg of selenium or placebo.	Prostate cancer selenium incidence	Risk of prostate cancer was lower in the intervention group than in the placebo group (RR, 0.37; P = .002).
Li 2000[28] n = 2,065 Duration: 3 years	Male HBs-Ag carriers (China)	Participants were randomized to receive 0.5 mg sodium selenite or placebo daily.	Liver cancer incidence	Liver cancer incidence was significantly lower in the group treated with selenium than in the placebo group (RR = 0.51, 95% CI = 0.34 - 0.77)
Duffield-Lillico 2003[32] Nutritional Prevention Cancer Trial (NPCT) n = 927 Duration: 7.5 years	Men with no history of prostate cancer (United States)	Participants were randomized to receive 200 mg/day of selenium or placebo.	Prostate cancer incidence	Selenium supplementation significantly decreased risk of prostate cancer. The protective effect of selenium supplementation on risk of prostate cancer greatest among those with a PSA levels ≤ 4 ng/mL and among those with a selenium baseline plasma level of ≤ 106.4 ng/mL.
Reid 2008[33] Nutritional Prevention Cancer (NPCT) n = 424 Duration: 6 years	High-risk dermatology patients with confirmed histories of nonmelanoma skin cancer (NMSC) (United States)	Participants were randomized into three treatment groups: 400 μg / selenium), 200 μg of selenium, or placebo	Total NMSC, total squamous cell carcinoma, total basal cell carcinoma and total cancer incidence	Risk of NMSC increased among those who took the 200 μg selenium. No difference in the 400 μg group. Treatment with 200 μg of selenium decreased total cancer incidence.

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TABLE 1.
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First Author, Study Name*	Population (Country)	Intervention	End Point	Results
Beta-Carotene				
Greenberg 1990[38] n = 1,805 Duration: 5 years	Patients who had had a recent nonmelanoma skin cancer (United States)	Participants randomized to receive either 50mg beta-carotene or placebo daily	First occurrence of a new basal cell or squamous cell skin cancer	No difference between the groups in the rate of occurrence of new nonmelanoma skin cancer. No significant difference between groups in the mean number of new nonmelanoma skin cancers per patient-year.
Heinonen 1994[35] Alpha-Tocopherol and Beta-Carotene (ATBC) Trial n = 29,133 Duration: 6.1 years	Male smokers 50 to 69 years of age (Finland)	Participants randomized to receive either 50mg alpha-tocopherol, 20mg beta-carotene, both agents, or placebo daily.	Lung cancer incidence, cancer incidence	Incidence of lung cancer was higher among the men who received beta carotene than among men who received placebo (change in incidence: 18%; 95% CI: 3-36%).
Omenn 1996[36] The Beta-Carotene and Retinol Efficacy Trial (CARET) n = 18,314 Duration: 4 years	Smokers, former smokers, and workers exposed to asbestos (United States)	Participants were randomized to receive 30mg beta-carotene and 25,000 IU retinol or placebo daily.	Lung cancer incidence; cancer incidence, mortality	The active-treatment group had an increased risk of lung cancer as compared with the placebo group. Study was stopped 21 months early because of findings.
Heinonen 1998[37] ATBC Trial n = 29,133 Duration: 6.1 years	Male smokers aged 50–69 years (Finland)	Participants received 50mg alpha-tocopherol, 20mg beta-carotene, both agents, or placebo daily	Total cancer incidence, prostate cancer incidence and prostate cancer mortality	Prostate cancer incidence decreased by 32% in the alpha-tocopherol group. Mortality from prostate cancer was 41% lower among alpha-tocopherol.
Lee 1999[78] The Women's Health Study n = 39,876 Duration: 4.1 years	Women aged 45 years or older (United States)	Participants were given either 600 IU of natural source vitamin E, 100mg aspirin, 50mg beta-carotene, all three agents, all three placebos, two agents and one placebo, or one agent and two placebos.	Invasive cancer incidence	Among women randomly assigned to receive beta-carotene or placebo, there were no statistically significant differences in incidence of cancer The beta-carotene component of the study was stopped early due to finding from previous studies.
Albanes 2000[39] ATBC Trial n = 29,133 Duration: 6.1 years	Male smokers aged 50–69 years (Finland)	Participants received 50mg alpha-tocopherol, 20mg beta-carotene, both agents, or placebo daily	Colorectal cancer incidence	Relative to control group, neither beta carotene nor alpha-tocopherol had a significant effect on colorectal cancer incidence

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TABLE 1.
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First Author, Study Name*	Population (Country)	Intervention	End Point	Results
Vitamin D				
Trivedi 2003[46] n = 2,686 Duration: 5 years	Healthy men and women 65-85 years of age (United Kingdom)	100,000 IU oral vitamin D3 supplementation or placebo every 4 months	Cancer incidence	Vitamin D3 supplementation had no significant effect on cancer incidence.
Wactawski-Wende 2006[48] Women's Health Initiative n = 36,282 Duration: 7 years	Healthy postmenopausal women 50 to 79 years of age (United States)	Participants randomized into one of two arms. The intervention arm received 1,000 mg of elemental calcium with 400 IU vitamin D3 or placebo	Colorectal cancer incidence	The incidence of invasive colorectal cancer did not differ significantly between women receiving calcium plus vitamin D supplementation and those assigned to placebo.
Lappe 2007[47] n = 1,179 Duration: 4 years	Healthy postmenopausal women over 55 living in a rural area (United States)	Population-based, double-blind, randomized placebo-controlled trial. Participants were randomized to receive 1400-1500 mg supplemental calcium alone, supplemental calcium plus 1100 IU vitamin D3/d (Ca + D), or placebo	Cancer incidence	Cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < .03).
Brunner 2011[49] Women's Health Initiative n = 36,282 Duration: 7 years	Healthy postmenopausal women 50 to 79 years of age (United States)	Participants were randomized to receive 1,000 mg elemental calcium with 400 IU vitamin D3 or placebo.	Cancer incidence and mortality	Incidence of invasive cancer did not differ between the two groups. Mortality did not differ between the two groups.

Abbreviations: RDA, US recommended daily allowance; RR, risk ratio; CI, confidence interval; HR, hazard ratio; NMSC, nonmelanoma skin cancer; PSA, prostate specific antigen; HBsAg, hepatitis B surface antigen.
*Study names included if applicable.

men with normal prostate serum antigen (PSA) levels at baseline resulted in a reduced incidence of prostate cancer. However, among men with elevated PSA levels at baseline, multivitamin use was associated with a slightly increased incidence of prostate cancer.[16] The Physicians Health Study II, a large randomized clinical trial, continues to examine the effects of multivitamins in preventing prostate, colorectal, and other cancers in healthy men (ClinicalTrials.gov, NCT00270647). Results from the Iowa Women's Health Study of older women, suggest that there is an increase in overall mortality with the use of multivitamins, vitamin B6, iron, magnesium, zinc, and copper.[17]

Single Agents

Vitamin C. Vitamin C (ascorbic acid) is a water-soluble antioxidant that is an essential nutrient for humans. All fruits and vegetables contain vitamin C, with high concentrations found in citrus fruits, cruciferous vegetables, and dark leafy greens. The dietary reference intake (DRI) estimated average requirement is 60 mg per day for women and 75 mg per day for men.[18] In the 1970s, Linus Pauling promoted the use of vitamin C to prevent the common cold, and later for the treatment of cancer. His results remain controversial, but popular interest in vitamin C is still high. To date, clinical trials examining the effects of vitamin C on cancer prevention have not shown benefit.[19,20]

Vitamin E. Vitamin E is a fat soluble antioxidant that acts as a free-radical scavenger. Nuts, seeds, vegetable oils, and green leafy vegetables are food sources high in vitamin E. The DRI estimated average requirement for vitamin E is 12 mg/ 22.4 IU per day and it is commonly found in multivitamin formulations.[18] Thus far, clinical trials have shown no benefit of vitamin E as a chemoprevention agent. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) found no benefit of vitamin E supplementation in men on the risk of prostate cancer; the trial was stopped early because of concern that vitamin E may increase the risk of prostate cancer.[21,22] Updated results from the SELECT trial report that this concern was warranted. After 7 years mean follow-up, supplementation with 400 IUs of vitamin E significantly increased the risk of prostate cancer.[23] Similarly, well-designed clinical trials among women have not shown benefit of vitamin E on the prevention of breast, lung, or colon cancer.[24,25]

Selenium. Selenium is a necessary trace mineral involved in metabolism and is a potent antioxidant. Food sources high in selenium include Brazil nuts, brewers yeast, and vegetables grown in selenium-rich soil. Other food sources include fish, shellfish, red meat, grains, eggs, chicken, and garlic. The current DRI for selenium is 45 μg per day for adults.[18] Results from the initial trials in Linxian, China led many to believe that selenium could be a beneficial chemopreventive agent. Additional trials in China reported that selenium supplementation lowered the incidence of liver cancer.[26-28] However, results from clinical trials in the United States examining the effect of selenium supplementation on the incidence of cancer have been inconsistent. Early trials reported that selenium supplementation led to a significant decrease in the incidence of prostate cancer, but recent trials have reported no benefits from supplementation.[21,22,29-31] The latest results from the SELECT trial, however, report a possible increase in prostate cancer risk from selenium supplementation, although this increase did not reach statistical significance.[23] The Nutritional Prevention of Cancer Trial (NPCT) aimed to examine the effect of selenium on the incidence of several cancers and total cancer mortality. While selenium supplementation did not reduce the incidence of nonmelanoma skin cancer, it was found to be protective against prostate, lung, and colorectal cancers, and significantly reduced total cancer incidence and total cancer mortality.[30-33]

Beta-carotene. Beta-carotene, a nutrient found in leafy vegetables and fruit of yellow and orange pigment, is also an antioxidant and a free radical scavenger. Beta-carotene is also commonly found in multivitamin and combination antioxidant dietary supplement formulations. Observational studies have shown an inverse association between dietary beta-carotene intake and lung cancer incidence in populations at high risk of developing lung cancer.[34] Based on these observations, large-scale clinical trials were conducted to determine the ability of supplemental beta-carotene to prevent lung cancer in high-risk populations.[35,36] Contrary to the study hypotheses, two trials[36,37] conducted among smokers and asbestos workers showed increased rates of lung cancer among those who received beta-carotene supplementation, and one of the trials also showed no significant difference in the incidence of prostate cancer.[37] Beta-carotene showed no effect in clinical trials testing its efficacy in skin and colon cancer prevention.[38,39] These findings suggest a cautious approach to translating observational findings to the clinical setting, and reinforce the need for well-conducted clinical trials to demonstrate the benefit or harm of natural products for cancer prevention. The US Preventive Services Task Force has concluded that beta-carotene supplementation is unlikely to provide clinical benefits and may cause harm to some groups.[40]

Vitamin D. Vitamin D is a fat-soluble vitamin that functions as a prohormone and regulates bone metabolism. The two major forms of vitamin D are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 is produced in the skin on exposure to ultraviolet radiation. Dietary sources of vitamin D include fatty fish (salmon, mackerel, sardines) and mushrooms. The Institute of Medicine recently published a report recommending a daily dose of 600 IUs of vitamin D.[41] A rapidly growing body of observational data suggests that higher vitamin D concentrations in the blood are associated with lower rates of multiple cancer types.[42-45] It is currently unknown whether changing an individual's vitamin D concentration over time is beneficial, or at what point in the life course this change may be important for cancer prevention. To date, the results of four clinical trials[46-49] have been published on the effects of

combined vitamin D and calcium supplementation on cancer incidence and/or mortality. Of these, only one trial reported a decrease in cancer incidence resulting from vitamin D and calcium supplementation.[47] The other trials reported no impact on total cancer incidence, colorectal cancer, or cancer mortality resulting from combined vitamin D and calcium supplementation.[46,48,49] Many clinical trials are ongoing to examine the effects of vitamin D supplementation on surrogate biomarkers for cancer, as well as cancer incidence, some with doses as high as 25,000 IUs per week (ClinicalTrials.gov). The Vitamin D and Omega-3 Trial (VITAL) is an ongoing trial examining the effects of vitamin D and omega-3 supplementation in women on a host of outcomes, including cancer incidence (ClinicalTrials.gov, NCT01169259). Recruitment for the study began in January 2010 and is continuing through 2011.

Botanicals

Clinical trials examining botanicals as chemopreventive agents are described in Table 2.

Green tea. There is a great deal of interest in the chemopreventive effects of green tea (*Camellia sinensis*), particularly in the catechin polyphenols components. Epidemiologic studies suggest that green tea consumption may reduce the risk of upper gastrointestinal tract cancers, lung cancer, hepatocellular cancer, and breast cancer in premenopausal women.[50,51] The most commonly studied polyphenol in the clinical trial setting is epigallocatechin-3-gallate (EGCG).[51] Green tea catechins act on multiple pathways, including oxidative stress, carcinogen elimination, and enzyme inhibition.[51] Green tea has historically been ingested as a tea, but chemoprevention applications typically use concentrated extracts. Currently there is no consensus on the necessary dose or duration of use. Pilot clinical trials of green tea have focused on effects on surrogate biomarkers, and have suggested potential benefit in oral, skin, cervical, and prostate cancer prevention[52-56]; these results need to be replicated. Trials are ongoing on the use of green tea for the prevention of breast cancer (www.ClinicalTrials.gov, NCT00917735, NCT00676793).

Soy. Soy, a complete protein source regarded as a staple of the East Asian diet, contains isoflavones that are of chemopreventive interest for their phytoestrogenic and antioxidant effects. Soy isoflavones can be administered via powder, extract, or in food; there is no standardized dose. The clinical trial evidence for soy as an effective chemopreventive strategy in food or supplement form has been mixed. There has been interest in the use of soy for breast cancer prevention, but little evidence suggests an effect.[57] There have been concerns of soy phytoestrogens acting as tumor promoters after a breast cancer diagnosis; a recent editorial suggests that this need not be a concern.[58] Studies on the effects of soy isoflavones on prostate cancer biomarkers, including PSA, have yielded mixed results.[59-61] An early phase study suggested that soy may decrease tumor progression in patients with low-grade prostate cancer.[62]

Curcumin. Curcumin, also known as turmeric or *Curcuma longa*, is a root commonly used as a culinary spice and is a major component of curry powders. Curcuminoids are the bioactive components of particular interest in chemoprevention for their antioxidant and anti-inflammatory effects, as well as their ability to inhibit activation of carcinogens by cytochrome enzymes.[63] There is no standardized dose at this time, and routes of administration can be via encapsulated powder, extracts, or in food. Curcumin is poorly absorbed and most research to date has focused on the prevention of colorectal cancer because of the direct contact with the colonic mucosa. There are limited clinical trial data. A primary prevention study suggested that curcumin may prevent the development of aberrant crypt foci in populations at high risk of colorectal cancer.[64] A small study in patients with adenomas suggested a possible reduction of polyp size and number with curcumin administration, whereas a study among patients with advanced colorectal cancer showed little effect on preventing disease progression.[65,66]

Fish Oil, Medicinal Mushrooms and Probiotics

A summary of clinical trials examining the use of fish oil, medicinal mushrooms, and probiotics are found in Table 3.

Fish Oils. Omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are polyunsaturated fatty acids contained in fish oils. These compounds have been shown to have cardioprotective effects and are of interest for cancer prevention for their ability to inhibit the formation of proinflammatory and procarcinogenic eicosanoids, such as prostaglandins. Typical doses

TABLE 2.
Clinical Trials Examining Botanicals as Chemoprevention Agents

First Author, Study Name*	Population	Intervention	End Point	Results
Green tea				
Katiyar 2000[52] n = 6 Duration: Punch biopsies were collected from each subject 24 hours after UV exposure	Healthy Caucasian male and females ages 25-55 yrs old (United States)	Different doses of GTP were topically applied 20 min before human buttock skin (sun-protected site) exposure to UV	Production of UVB-induced CPDs in the skin	Topical treatment with 1 mg/skin site/50 μl acetone GTP inhibited CPD formation in epidermis ($P<.0005$).
Jatoi 2003[53] n = 42 Duration: 6 months	Men (mean age: 75 years) with asymptomatic, biopsy-proven prostate cancer, and clinical evidence of androgen independence (United States).	One gram of green tea powder six times a day	Tumor response as measured by PSA levels	63% of participants experienced disease progression. Only one patient exhibited tumor response, and the decrease was not sustained beyond 2 months.
Choan 2005[54] n = 19 Duration: 5 months	Men aged 61-84 (median age: 76 yrs) with hormone refractory prostate cancer (Canada)	GTE capsules (250 mg) twice daily	Disease progression or evidence of radiological progression	All of the subjects experienced disease progression by month 5.
Bettuzzi 2006[55] n = 6 Duration: 1 year	Caucasian men between the ages of 45-75 with high-grade prostatic intraepithelial neoplasia lesion (Italy)	Double-blind, placebo-controlled study. Participants received either placebo or 3 200mg GTC capsules daily	Prevalence of prostate cancer	The prevalence of prostate cancer was significantly lower in the GTC-treated group ($P<.01$).
Tsao 2009[56] n = 41 Duration: 12 weeks	Men and women ages 33-76 with histologically confirmed, high-risk OPL (United States)	Subjects were randomized to one of four groups: GTE at 500, 750, or 1,000 mg/m^2 or placebo 3 times daily for 12 weeks	Clinical and histologic response of high-risk OPLs at 12 weeks	The OPL clinical response rate was higher in all GTE arms but not statistically significant.
Soy				
Adams 2004[59] Soy Isoflavone Prevention Trial (SIP) n = 81 Duration: 12 months	Men 64-80 years of age enrolled in a larger clinical trial and with adenomatous polyps detected on colonoscopy (United States).	Double-blinded, parallel-arm, randomized trial; participants assigned to consume either a soy protein drink with isoflavins (ISO) or placebo (−ISO).	Serum PSA concentrations	There was no difference in mean serum PSA level between treatment groups.
deVere 2004[60] n = 62 Duration: 6 months	Men with histologically confirmed prostate cancer and two consecutive elevated PSA readings. range, 61.4 to 89.3 (United States)	Non-randomized, open-label study. Participants consumed 5 g of the Genistein combined polysaccharide extract daily	PSA response	None of the 52 men evaluable at month 6 had a complete response; 35 had progression, 8 had stable PSA levels, and 9 had a partial response.

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TABLE 2.
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First Author, Study Name*	Population	Intervention	End Point	Results
Kumar 2004[61] n = 76 Duration: 12 weeks	Early stage prostate cancer patients with a Gleason score of 6 or below, between ages 45-85 yrs (United States)	Participants randomized to receive either a soy protein beverage supplement or isocaloric placebo.	Changes in total and free PSA and hematological-serum steroid hormonal biomarkers	No statistically significant differences in the change in serum steroid hormone concentrations between the two groups.
Hamilton-Reeves 2008[62] n = 58 Duration: 6 months	Patients with preneoplastic lesions or low-grade prostate cancer with Gleason scores of 6 or below (United States)	Participants were randomly assigned to receive one of three protein isolates twice daily: 1) soy protein (SPI +, 107 mg isoflavones/d); 2) alcohol-washed soy protein (SPI–, <6 mg isoflavones/d); or 3) milk protein (MPI).	Antigen expression, serum PSA concentrations, and prostate cancer incidence	Bax expression was lower in prostate biopsies in the SPI-group compared with the MPI group after 6 months (P=.03). Among the 49 men evaluable at month 6, the incidence of prostate cancer incidence was more than 6 times higher in the MPI group than in the combined soy groups (P = .01).
Curcumin				
Sharma 2001[66] n = 15 Duration: Treated until disease progression	Men and women with histologically confirmed adenocarcinoma of the colon or rectum refractory to standard chemotherapies (United Kingdom)	Subjects given different doses of a soft gelatin capsules containing curcuminoids and assigned to treatment groups 2, 4, 6, 8, or 10 capsules	Lymphocytic total GST activity and leukocytic M_1G levels	Leukocytic M_1G levels were constant within each patient and unaffected by treatment.
Cruz-Correa 2006[65] n = 5 Duration: 9 months	Caucasian men and women with Familial Adenomatous Polyposis (United States)	Participants received curcumin 480 mg and quercetin 20 mg orally 3 times a day	Number and size of polyps at the end of treatment	Polyp number decreased by 60.4% the mean decrease in polyp size with treatment was 50.9%

Abbreviations: GTP, green tea phenol; CPDs, cyclobutane pyrimidine dimers; GTCs, green tea catechins; OPL, oral premalignant lesions; GTE, green tea extract; GST, glutathione S-transferase.
*Study names included if applicable.

range from 1 to 4 g/day and are usually ingested via capsules or liquid form. Clinical trials to date suggest that EPA and DHA may protect against colorectal cancer in high-risk populations.[67,68] VITAL is an ongoing trial assessing the potential benefits of fish oil supplementation on overall cancer risk (www.ClinicalTrials.gov, NCT01169259).

Medicinal mushrooms. Medicinal mushrooms, including *Ganoderma lucidum, Coriolus versicolor,* and maitake *Grifola frondosa*), are commonly found in Asian traditional pharmacopeias. Medicinal mushrooms may exert chemopreventive effects through their polysaccharides, which have been shown to enhance immune function, as well as their secondary metabolites, which may affect pathways related to apoptosis, angiogenesis, metastasis, cell cycle regulation, and signal transduction cascades.[69] Medicinal mushrooms are commonly ingested via encapsulated powders, extracts, and

TABLE 3.
Clinical Trials Examining the Use of Fish Oil, Medicinal Mushrooms, and Probiotics as Chemoprevention Agents

First Author, Year	Population	Intervention	End Point	Results
Fish Oil				
Bartoli 1993[67] n = 40 Duration: 30 days	Males and females with sporadic adenomatous colorectal polyps (Italy)	Double-blind randomized control trial. Subjects were divided into 4 groups. Three groups were given capsules. Each capsule contained EPA, DHA and Tocopherol.	Cell proliferation of the rectal crypt cells	Total labeled and mean index for the high-crypt region was lower in the treatment groups; effect more pronounced at higher dosages.
West 2010[68] n = 55 Duration: 6 months	Males and females 18-74 years of age with familial adenomatous polyposis (United Kingdom)	Randomized, double-blind, placebo-controlled trial. Subject were randomized to receive two soft-gel capsule containing 500 mg of omega 3 polyunsaturated EPA in free fatty acid form (EPA-FFA) or placebo twice daily for 6 months.	Number and size of rectal polyps	Subjects taking EPA experienced a 22.4% decrease in polyp number compared with placebo. Subjects in the EPA-FFA treatment group experienced a 29.8% overall decrease in polyp size compared with the placebo group
Medicinal Mushrooms				
Mitomi 1992[70] n = 448 Duration: 5 years	Males and females with primary carcinoma of the colon and rectum under 75 years of age (Japan)	Randomized, controlled trial. Subjects were divided into two groups.Those in the treatment group were given PSK (3g/day) orally.	Colorectal tumor recurrence and disease-free survival	3-year survival was 85.5% for the PSK group and 79.2% for the control group (P = .01). In patients with colon cancer, overall survival was significantly higher in the group treated with PSK (P = .04).
Gao 2003[71] n = 34 Duration: 12 weeks	Males and females with histologically confirmed, advanced-stage cancer (China)	Subjects were given 1800 mg Ganopoly, three times daily orally before meals.	Immune parameters (cytokines), T-cell subsets, mitotic response to PHA, and NK activity	There was a significant increase in the mean plasma concentrations of IL-2, IL-6, and IFN-g. Levels of IL-1 and TNF-a were significantly decreased (P < .05). Treatment with Ganopoly resulted in a significant increase in the mean NK activity.
Kodama 2003[72] n = 10	Cancer patients (Japan)	Patients were administered maitake D-fraction.	NK cell activity, numbers of CD4+ , CD8+, level of serum soluble interleukin-2 receptor (sIL- 2R), and expression of tumor markers	Maitake D-fraction decreased expression of tumor markers, and increased NK cell activity in all patients examined.
Probiotics				
Ishikawa 2005[74] n = 398 Duration: 4 years	Men and women 40-65 years of age. Subjects had had at least 2	Subjects were randomized into four groups: regular intake	Colorectal cancer diagnosed by colonoscopy	The administration of *L. casei* and wheat bran did not result in any

(*Continued*)

TABLE 3.
(Continued)

First Author, Year	Population	Intervention	End Point	Results
	colorectal tumors removed endoscopically within 3 months before recruitment	of wheat bran biscuits, regular intake of *L.casei* preparation, regular intake of both and no treatment.		differences in the development of new colorectal tumors. In *L. casei* group there was a lower occurrence rate of tumors with a grade of moderate or severe atypia, OR: 0.65 (95% CI: 0.43-0.98).
Klein 2008[75] n = 26 Duration: 5 weeks	Men and females (mean age: 25 years) in good general health (Germany)	Placebo-controlled, crossover study. The first group consumed 300 g/day of yoghurt supplement containing probiotic strains *L. acidophilus* 74-2 and *B. lactis* 420 and the second group consumed a placebo product. The two groups were crossed during the following 5-week period.	Immunologic parameters, including number of lymphocytes, monocytes, granulocytes, and T-cell expression	Cell counts of lymphocytes, monocytes, granulocytes, and the expression of various CD cells and HLA-DR did not change throughout the study.

Abbreviations: EPA, eicosapentaenoic acid; 5-FU, 5-fluorouracil; FFA, free fatty acid; PSK, polysaccharide-K; PHA, phytohemmagglutinin; NK, natural killer; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor.

teas. Clinical trial research is in the early stages and preliminary studies have shown protective benefits including increasing immune function and preventing recurrence of cancer.[70-72]

Probiotics

Probiotics, such as *Lactobacillus sp.*, are live microorganisms found in dietary supplements and fermented food sources, such as yogurt and kefir, which possess possible chemopreventive benefits for the gastrointestinal tract.[73] Doses vary depending on the type of organism and are typically quantified by the number of living organisms per capsule, or colony forming unit (CFU) per capsule. Probiotics are hypothesized to confer their chemopreventive benefit by altering the gut microbiota and subsequently inhibiting/inducing colonic enzyme systems, controlling growth of harmful bacteria, improving immune function, and stimulating the production of active anticancer metabolites. In a trial of patients with a history of colorectal cancer, the occurrence of tumors with moderate and severe atypia was lower in the group receiving *L. casei* supplementation.[74] A clinical trial among healthy individuals suggested increased immune response with probiotics.[75] More research is needed to fully understand the chemopreventive role of probiotics.

Implications for Oncology Clinicians

Individuals use natural products for a variety of reasons, including cancer prevention and preventing cancer recurrence. It is important for health care providers to discuss use of natural products with their patients so that they can be counseled appropriately. Towards this aim, algorithms and guidelines have been developed for clinicians to use when counseling patients on the use of natural products and other complementary therapies.[76,77] There are a number of reputable online resources for health care providers to use to investigate specific natural products, including the National Center for Complementary and Alternative Medicine (www.nccam.nih.gov), the National Cancer

Institute's Office of Cancer Complementary and Alternative Medicine (www.cancer.gov/cam), US National Library of Medicine (www.nlm.nih.gov/medlineplus), American Institute for Cancer Research (www.aicr.org), and Natural Medicines Comprehensive Database (www.naturaldatabase.therapeuticresearch.com).

Based on evidence to date, it is not possible to recommend specific natural products as reliable and effective chemoprevention strategies. Clinicians should encourage their patients to use proven chemoprevention strategies and to follow lifestyle modifications to reduce their cancer risk. The reader is referred to the cancer prevention strategies published by the American Institute of Cancer Research.[79]

Clinicians can also suggest that their patients participate in clinical trials, when appropriate, to build the evidence base. Ongoing trials can be found at www.ClinicalTrials.gov.

For patients who are already using natural products, clinicians can inquire about their motivation for use, and counsel them using the current recommendations. Many patients use natural products with the goal of maintaining and/or improving overall health and wellness. This can be a good opportunity to discuss the benefits of other healthy behaviors, such as cancer screening, maintaining a healthy diet, being physically active, and maintaining a healthy body size.

For patients who chose to use natural products, clinicians can advise them to use high-quality products that are produced under high levels of quality assurance; although this can be difficult to do given that the natural product industry is not regulated.

Implications for Special Populations

Special populations, including individuals at high risk of developing cancer, individuals receiving cancer treatment, and individuals who have completed treatment, commonly use natural products. There is limited evidence to date on the effectiveness of natural products preventing cancer or cancer recurrence. Certain populations, including pediatric and geriatric populations, may be high users of natural products, using natural products for other health concerns. These patients should be counseled on potential effects, lack of effects, as well as drug interactions.

Conclusion

There is great potential for specific dietary supplements to be effective chemopreventive agents. However, to date some agents have shown promise while others have not. No agents have been proven to be effective against all cancers, and it is highly unlikely that such an agent will be identified. Until stronger evidence exists, clinicians can encourage their patients to engage in healthy behaviors, eg, cancer screening, maintaining a healthy diet, achieving a healthy body size, and being physically active.

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