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Natural Products for Cancer Prevention

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Abstract

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 specifically for cancer prevention, they should be counseled on the current guidelines, as well as their options for other cancer prevention strategies.

Keywords

cancer; cancer prevention; multivitamins; vitamins; botanicals; medicinal mushrooms; probiotics; natural products; clinical trials; review

Individuals born in the US 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 which 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

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effectiveness of natural products for cancer prevention, including vitamins and minerals, botanicals, probiotics, and other agents of interest. The use of natural products has increased in the United States in recent years. 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 disease, preventing disease, maintaining health, and promoting wellness. The evidence base 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, we know that 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 feel 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 Food and Drug Administration (FDA), 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 yet exist regarding the appropriate formulation, dose, duration, and cancer type for promising 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 upfront that many of the results presented in the tables are based upon 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 revealed 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 men with normal PSA levels at baseline resulted in reduced prostate cancer incidence. Among men with elevated PSA levels at baseline however, multivitamin use was associated with a slightly increased prostate cancer incidence.[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). Of note, recent results from the Iowa Women's Health Study, a cohort 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 for women is 60 mg per day and for men is 75 mg per day.[18] Beginning 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 and claims 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 vitamin E DRI estimated average requirement 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 and the trial was stopped early due to concern of vitamin E increasing prostate cancer risk.[21,22] Recent updated results from the SELECT trial demonstrate 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 in adults is 45 μg per day.[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 risk of liver cancer incidence, [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 significant decrease in the incidence of prostate cancer, but more 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, squamous or basal cell carcinoma, 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 prostate cancer incidence.[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 U.S. Preventive Services Task Force has concluded that beta-carotene supplementation is unlikely to provide important clinical benefits and that it 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 upon 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 lifecourse 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 breast cancer prevention (www.ClinicalTrials.gov NCT00917735, NCT00676793).

Soy—Soy, a complete protein source regarded as a staple of the East Asian diet, contains isoflavones which are of chemopreventive interest for their phytoestrogenic and antioxidant effects. Soy isoflavones can be administered via powder, extract or in food and 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 great interest in the use of soy for primary breast cancer prevention, but little evidence thus far suggesting 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 prostate serum antigen (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 of the research to date has focused on colorectal cancer prevention because of the direct contact with the colonic mucosa. There are limited clinical trial data. A primary prevention study suggests 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 Mushromms and Probiotics

A summary of clinical trials examining the use of fish oil, medicinal mushsrooms 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 range from one to four grams per 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] The Vitamin D and Omega-3 Trial (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 teas. The clinical trial research is in the early stages and preliminary studies have shown protective benefits including increasing immune function, and preventing recurrence.[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 patient 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. See Table 4 for a list of the most recent cancer prevention strategies published by the American Institute of Cancer Research.[78]

Clinicians can also suggest that their patients participate in clinical trials, when appropriate, in order 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, though 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. Reliable resources for clinicians include 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) and Natural Medicines Comprehensive Database (www.naturaldatabase.therapeuticresearch.com).

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 other healthy behaviors, including cancer screening, maintaining a healthy diet, achieving a healthy body size and being physically active.

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Table 1

Clinical Trials Examining Vitamins and Minerals as Chemoprevention Agents

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
Multivitamins and combinations						
Blot 1993 [15] Nutrition Intervention Trial	29,584	Health individuals aged 40–69 with no history of esophageal or stomach cancer (China)	Participants were randomized to receive either two of the four following combinations, all four combinations, or a placebo: zinc and retinol; riboflavin and niacin; vitamin C and molybdenum; beta-carotene, vitamin E and selenium.. Doses of each nutrient ranged from one to two times U.S. Recommended Daily Allowances (RDAs).	5.25 years	Cancer incidence (esophagus, 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). Supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum did not significantly cancer mortality, or cancer incidence.
Meyer 2005 [16] SU.VI.MAX Trial	5,141	Healthy men aged 45–60 (Canada)	Randomized, double-blind placebo controlled trial. Participants received either a placebo or a capsule containing acombination of 120 mg vitamin C, 30 mg alpha-tocopherol, 6 mg beta-carotene, 100 μg selenium and 20 mg zinc every day for 8 years.	8 years	Prostate cancer incidence	Nonsignificant reduction of the rate of prostate cancer overall. Stratified analysis showed that 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). In men with elevated PSA levels at baseline, selenium supplementation increased prostate cancer incidence although this result was only borderline statistically significant (HR = 1.54; 95% CI = 0.87–2.72).
Vitamin C						
Moertel 1985 [19]	100	100 men and women with advanced colorectal cancer (United States)	Participants received either 10g of vitamin C or placebo daily	Median duration was 2.5 months with vitamin C and 3.6 months with placebo	Progression of advanced colorectal cancer and survival	Vitamin C supplementation did not result in any significant difference in disease progression or survival. No patients with measurable disease experience improvement after treatment with Vitamin C.
Gaziano 2009 [20] The Physician's Health Study II	14,641	Male physicians aged 50 years or older (United States)	Randomized, double-blind, placebo controlled factorial trail. Participants randomized to receive either 1) 400 IU of vitamin E every other day and 500 mg/dl of vitamin C daily; 2) 400 IU of	Mean follow up 8 years	Total prostate cancer, total cancer, for vitamin E component; total cancer, incident colorectal cancer for vitamin C component. Total mortality and cancer mortality for both.	Vitamin E did not significantly affect the incidence of prostate cancer (active vs. placebo vitamin E HR=0.97; 95% CI=0.85–1.09), or total cancer (active vs. placebo vitamin E HR=1.04; 95% CI=0.95–1.13), There was no significant effect of vitamin C supplementation on total

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
			vitamin E every other day and placebo vitamin C daily; 3) placebo vitamin E every other day and 500 mg/dl of vitamin C placebo daily; or 4) placebo Vitamin E and C.			cancer incidence (active vs. placebo vitamin CHR = 1.01; 95% CI = 0.92–1.10; P = .86) or prostate cancer incidence (active vs. placebo vitamin C HR = 1.02; 95% CI = 0.90–1.15; P = .80). Neither vitamin E nor vitamin C had a significant effect on colorectal, lung, or other site-specific cancers.
Vitamin E						
Lonn 2005 [24] Heart Outcomes Prevention Evaluation (HOPE); HOPE – The Ongoing Outcomes (HOPE-TOO)	HOPE: 9,541 HOPE-TOO: 7,030	Men and women at least 55 years old with vascular disease or diabetes mellitus (International)	Randomized placebo controlled trial. Participants randomized to receive 400 IU/day of Vitamin E or placebo.	Mean duration of follow-up was 7 years.	Cancer incidence and cancer mortality.	There were no significant differences in incident cancers between the Vitamin E group and the placebo group (RR = 0.94; 95% CI = 0.84–1.06; P = 0.30) or in cancer mortality (RR=0.88; 95% CI: 0.71–1.09)
Lee 2005 [25] The Women's Health Study	39,876	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.	Average follow-up of 10.1 years	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 (RR = 1.01; 95% CI = 0.94–1.08; P = .87), breast cancer (RR = 1.00; 95% CI = 0.90–1.12; P = .95), lung cancer (RR = 1.09; 95% CI = 0.83–1.44; P = .52), or colon cancers (RR = 1.00; 95% CI = 0.77–1.31; P = .99). Vitamin E supplementation had no significant effect on cancer mortality (RR= 1.12, 95% CI 0.95–1.32).
Lipmann (2009)[21] Selenium and Vitamin E Cancer Prevention Trial (SELECT)	35,533	Healthy men age 55 and older (age 50 and older if African American) with normal digital rectal exams and prostate specific antigens <4 ng/ml (United States, Canada, Puerto Rico)	Randomized, placebo-controlled trial. Participants were randomized into four groups 1) 200 μg/day of selenium, 2) 400 IU/day vitamin E, 3) Vitamin E and selenium supplements, or 4) placebo	Median follow up 5.5 years	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 (HR: 1.13 (99% CI, 0.95–1.35 for vitamin E; 1.04 (99% CI, 0.87–1.24) for selenium; and 1.05 (99% CI, 0.88–1.25) for selenium and _ vitamin E all vs placebo. There were no significant differences) in any other prespecified cancer end points.
Klein (2011) Selenium and Vitamin E Cancer Prevention Trial (SELECT)[23]	35, 533	Healthy men age 55 and older (age 50 and older if African American) with normal digital rectal exams and prostate specific antigens <4 ng/ml (United States, Canada, Puerto Rico)	Randomized, placebo-controlled trial. Participants were randomized into four groups 1) 200 μg/day of selenium, 2) 400 IU/day vitamin E, 3) Vitamin E and selenium supplements, or 4) placebo	Median 7 years	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=0.008). Supplementation with both selenium and combination selenium and vitamin E resulted in a nonsignificant increase in prostate cancer risk. (HR: 1.09; 99% CI: 0.93–1.27, P=0.18 for selenium; HR: 1.05; 99% CI: 0.89–

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
						1.22, p=0.46 for selenium and Vitamin E respectively).
Selenium						
Yu 1991 [26]	2,474	Male and female first-degree relatives of liver cancer patients (China)	Participants were randomized to receive 200 μg selenium or placebo daily.	2 years	Liver cancer incidence	Ten cases in the selenium and 13 cases in the placebo group were observed (RR = 0.55; 95% CI = 0.24 – 1.25).
Yu 1997[27]	226	Male and female Hepatitis B Surface Antigen (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	8 years	Liver cancer incidence	Eleven cases were detected in the placebo group and four cases in the selenium group (RR = 0.36; 95% CI = 0.12 – 1.11).
Clark 1996 Nutrition Prevention of Cancer Trial (NPCT)[30]	1312	Men and women 18–80 year with a history of basal cell or squamous cell skin carcinomas (United States).	A multicenter, double-blind, randomized, placebo-controlled trial. Participants were randomized to receive 200 μg of selenium or placebo. Patients were treated for a mean (SD) of 4.5 (2.8) years	A mean of 6.5 years	Incidence of basal and squamous cell carcinomas of the skin, prostate, lung, and colorectal cancer. all-cause mortality, total cancer mortality, and total cancer incidence.	Selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer: relative risk(RR):1.10,95% CI:, 0.95–1.28),;(RR: 1.14; 95% CI, 0.93–1.39) for basal and squamous cell carcinoma, respectively. Patients treated with selenium had a significant reductions in total cancer mortality (RR, 0.50; 95% CI, 0.31–0.80), total cancer incidence, (RR, 0.63; 95% CI, 0.47–0.85]), and incidences of lung, colorectal, and prostate cancers. The trial was stopped early because of the reductions in total cancer mortality and cancer incidence in the group treated with selenium,
Clark 1998[31] Nutrition Prevention of Cancer Trial (NPCT)	974	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 200 μg of selenium or placebo. Patients were treated for a mean (SD) of 4.5 (2.8) years	A mean of 6.5 years	Prostate cancer incidence	Lower risk of prostate cancer experienced among the intervention group than the placebo group (RR = 0.37; P = 0.002).
Li 2000 [28]	2,065	Male HBs-Ag carriers (China)	Participants were randomized to receive 0.5 mg sodium selenite or placebo daily.	3 years	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 of Cancer Trial (NPCT)	927	Men with no history of prostate cancer (United States)	200 μg/day of selenium in 0.5-g high-selenium or placebo	Mean follow-up 7.5 years	Prostate cancer incidence	Selenium supplementation significantly decreased the risk of prostate cancer incidence (RR = 0.51; 95% CI = 0.29–0.87, P = 0.002). The protective effect of selenium

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
						supplementation on risk of prostate cancer incidence is greatest among those with a PSA ≤ 4 ng/mL (RR = 0.35; 95% CI = 0.13–0.87, P = 0.01) and among those with a selenium baseline plasma level of ≤ 106.4 ng/mL (RR = 0.14; 95% CI = 0.02–0.59, P = 0.002).
Reid 2008[33] Nutritional Prevention of Cancer (NPCT)	424	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	6 years	Total NMSC, total squamous cell carcinoma, total basal cell carcinoma and total cancer incidence	The risk of NMSC increased among those who took the 200 μg selenium (HR = 1.51; 95% CI = 1.13–2.04, P < 0.006). No difference in risk of NMSC was shown at the 400 mcg group (HR = 0.95; 95% CI = 0.69–1.20, P = 0.51). Treatment with 200 μg of selenium decreased total cancer incidence (RR= 0.75 = 95% CI: 0.56–0.99)
Beta-Carotene						
Greenberg 1990 [38]	1,805	Patients who had had a recent nonmelanoma skin cancer (United States)	Participants randomized to receive either 50 mg beta-carotene or placebo daily	Up to 5 years of follow-up	First occurrence of a new basal cell or squamous cell skin cancer	After five years of follow-up, there was no difference between the groups in the rate of occurrence a new nonmelanoma skin cancer in (RR = 1.04; 95 % CI = 0.89 – 1.21, P = 0.63). No significant difference between treatment and control groups in the mean number of new nonmelanoma skin cancers per patient-year (RR = 1.07; 95% CI = 0.91 – 1.24; P = 0.42).
Heinonen 1994 [35] ATBC Trial	29,133	Male smokers 50 to 69 years of age (Finland)	Participants randomized to receive either 50 mg alpha-tocopherol, 20 mg beta-carotene, both agents, or placebo daily	Median 6.1 years of follow up	Lung cancer incidence, cancer incidence	Higher incidence of lung cancer among the men who received beta carotene than among those who did not (change in incidence, 18%; 95 percent confidence interval, 3 to 36 %). No significant change in lung cancer incidence among men receiving alpha-tocopherol. Supplementation with beta carotene and alphatocopherol did not significantly impact total cancer incidence.
Omenn 1996 [36] The Beta-Carotene and Retinol Efficacy Trial (CARET)	18,314	Smokers, former smokers, and workers exposed to asbestos (United States)	Participants were randomized to receive 30 mg beta-carotene and 25,000 IU retinol or placebo daily	Mean of 4 years	Lung cancer incidence; cancer incidence, mortality	The active-treatment group had an increased risk of lung cancer as compared with the placebo group (RR = 1.28; 95% CI = 1.04 – 1.57;P = 0.02). There were no statistically significant differences in the risks of other types of cancer. Study was

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
						stopped 21 months early because of findings.
Heinonen 1998 [37] Alpha-Tocopherol and Beta-Carotene (ATBC) Trial	29,133	Male smokers aged 50–69 years (Finland)	Participants received 50 mg alpha-tocopherol, 20 mg beta-carotene, both agents, or placebo daily	Median 6.1 years of follow up	Total cancer incidence; prostate cancer incidence and prostate cancer mortality	Prostate cancer incidence decreased by 32% (95% CI= −47% to −12%) in the group receiving alpha-tocopherol compared with those not receiving it. Mortality from prostate cancer was 41% lower (95% CI = −65% to −1%) among men receiving alpha-tocopherol. Supplementation with beta carotene did not significantly impact prostate cancer incidence or prostate cancer mortality.
Lee 1999 [78] The Women's Health Study	39,876	Women aged 45 years or older (United States)	Participants were given either 600 IU of natural source vitamin E, 100 mg aspirin, 50 mg beta-carotene, all three agents, all three placebos, two agents and one placebo, or one agent and two placebos. All treatment given on alternate days.	Mean 4.1 years	Invasive cancer incidence	Among women randomly assigned to receive β-carotene or placebo, there were no statistically significant differences in incidence of cancer (RR = 1.03; 95% CI = 0.89 – 1.18; P = 0.73) Beta-carotene component of study was stopped early after median treatment of 2.1 years due to findings from previous studies.
Albanes 2000 [39] ATBC Trial	29,133	Male smokers aged 50–69 years (Finland)	Participants received 50 mg alpha-tocopherol, 20 mg beta-carotene, both agents, or placebo daily	Median 6.1 years of follow up	Colorectal cancer incidence	Relative to control group, neither beta carotene nor alpha-tocopherol had a significant effect on colorectal cancer incidence Beta carotene (RR = 1.05, 95% CI 0.75–1.47; log-rank test p = 0.78): Alpha-tocopherol (RR = 0.78; 95% CI = 0.55–1.09).
Vitamin D						
Trivedi 2003[46]	2,686	Healthy men and women aged 65–85 (United Kingdom)	100,000 IU oral vitamin D3 supplementation or placebo every four months	5 years	Cancer incidence	Vitamin D3 supplementation had no significant effect on cancer incidence (any cancer age-adjusted RR = 1.09; 95% CI = 0.86 – 1,36), even when stratified by sex (Males: any cancer age-adjusted RR = 1.11; 95% CI = 0.87 – 1.42; Females: any cancer age-adjusted RR = 0.95; 95% CI = 0.54 – 1.68).
Wactawski-Wende 2006 [48] Women's Health Initiative	36,282	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.	7 years	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 (HR = 1.08; 95% CI = 0.86–1.34, P = 0.51).

First Author Year, Study Name*	Number (n)	Population (Country)	Intervention	Duration	End Point	Results
Lappe 2007[47]	1,179	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	4 years	Cancer incidence	Cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < 0.03). Unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca− only groups were 0.402 (P = 0.01) and 0.532 (P = 0.06), respectively. Treatment and serum 25-hydroxy vitamin D concentrations were significant, independent predictors of cancer risk.
Brunner 2011 Women's Health Initiative[49]	36,282	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.	7 years	Cancer incidence and mortality	Incidence of invasive cancer did not differ between the two groups (HR = 0.98; CI = 0.90, 1.05, unweighted P = 0.54]. Mortality did not differ between the two groups (HR = 0.90 (0.77, 1.05).

*Study Names included if applicable

Abbreviations: RR: Risk Ratio, CI: Confidence Interval, HR: Hazard Ratio NMSC: Nonmelanoma skin cancer,

Table 2

Clinical Trials Examining Botanicals as Chemoprevention Agents

First Author Year, Study Name*	Number (n)	Population	Intervention	Duration	End Point	Results
Green tea						
Katiyar 2000 [52]	6	Healthy Caucasian male and females ages 25–55 yrs old (United States)	Skin sites were exposed to 0.5, 1.0, 2.0, or 4.0 MED of UVB irradiation. Different doses of green tea polyphenols (GTP) ranging from 1–4 mg/skin site/50 μl acetone were topically applied 20 min before human buttock skin (sun-protected site) exposure to UV.	24 hours after UV exposure, six skin punch biopsies were collected from each subject	Production of UVB-induced cyclobutane pyrimidine dimers (CPDs) in the skin	Topical treatment with 1 mg/skin site/50 μl acetone GTP inhibited CPD formation in epidermis by 81, 70, 60, and 60% at 0.5, 1.0, 2.0, and 4.0 minimal erythema dose of UV exposure, respectively ($p<0.0005$) Treatment with varying doses of GTP decreased CPD formations in a dose-dependent manner.
Jatoi 2003 [53]	42	Men with asymptomatic prostate carcinoma, biopsy-proven evidence of malignancy, and clinical evidence of androgen independence. Mean age 75 years (United States).	One gram of green tea powder mixed with cold or warm water six times a day.	6 months	Tumor response as measured by PSA levels	The median time on the study was one month, 63% of participants experienced disease progression. Only a single patient exhibited tumor response, and the decrease was not sustained beyond two months.
Choan 2005 [54]	19	Men aged 61–84 (Median age: 76) with hormone refractory prostate cancer (Canada)	Green tea extract capsules (250 mg) twice daily	No patient exceeded 5 months of treatment	Disease progression as defined by a PSA level rise of greater than 25% over baseline over a 2-month period or evidence of radiological progression	All of the subjects experienced disease progression by month 5. Of the subjects who consumed green tea for at least 2 months, 9 had progressive disease within two months, and the remaining six experienced disease progression from 3–5 months.
Bettuzzi 2006 [55]	60	Caucasian men ages 45–75 with high-grade prostatic intraepithelial neoplasia lesions (Italy)	Double-blind, placebo-controlled study. Participants received either placebo or 3 200 mg Green Tea Catechins (GTCs) capsules daily	1 year	Prevalence of prostate cancer	One cancer was diagnosed among the 30 GTCs-treated men whereas nine cancers were diagnosed among the 30 placebo-treated men ($p<0.01$)
Tsao 2009 [56]	41	Men and women ages 33–76 (Median: 57) with histologically-confirmed, high-risk oral premalignant lesions (OPL) (United States)	Subjects were randomized to one of four groups: green tea extract (GTE) at 500, 750, or 1,000 mg/m^2 or placebo thrice daily for 12 weeks	12 weeks	Clinical and histologic response of high-risk OPLs at 12 weeks	The OPL clinical response rate was higher in all GTE arms (n = 28; 50%) versus placebo (n = 11; 18.2%) but the difference did not reach statistical significance (P = 0.09) The histological response rate was 21.4% in the GTE arms versus 9.1% in the placebo group (P=0.65).
Soy						
Adams 2004 [59], Soy Isoflavone Prevention Trial (SIP)	81	Men aged 64 – 80 years enrolled in a larger clinical trial with adenomatous polyps detected on	Double-blinded, parallel-arm, randomized trial in which participants were assigned to consume either a soy protein	12 months	Serum PSA concentrations	There was no difference in mean serum PSA level between treatment groups.

First Author Year, Study Name*	Number (n)	Population	Intervention	Duration	End Point	Results
		colonoscopy.. Men were not hormone users and had (United States).	drink providing 83 mg/day isoflavones (+ISO) or a similar drink with isoflavones removed (−ISO).			
deVere 2004 [60]	62	Men with histologically-confirmed prostate cancer and two consecutive elevated PSA readings. Mean age 73.6 years, range (61.4 to 89.3). (United States)	Non-randomized, open-label study. Participants consumed 5 g of the Genistein combined polysaccharide (GCP) extract daily containing 450 mg/day of genistein, and 450 mg/day of other aglycone isoflavones.	6 months	PSA response	None of the 52 men evaluable at month 6 had a complete response; 35 experienced progression, 8 had stable PSA levels, and 9 had a partial response. Only one patient had a PSA decrease greater than 50% (1.9% of cohort, 95% CI: 0.1%–10.3%).
Kumar 2004 [61]	76	Early-stage prostate cancer patients with a Gleason score of 6 or below, between ages 45–85 (United States)	Participants randomized to receive either a soy protein beverage supplement containing 0 mg of genistein or isocaloric placebo for a 12 week period	12 weeks	Changes in total and free PSA and hematological-serum steroid hormonal biomarkers	There were no statistically significant differences in the change in serum steroid hormone concentrations between the two groups. The mean changes in PSA levels between the two groups were not statistically significant.
Hamilton-Reeves 2008 [62]	58	Patients with preneoplastic lesions (n = 53) or low-grade prostate cancer with Gleason scores of 6 or below (n = 5). Average age was 68 years (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).	6 months	Antigen expression, serum PSA concentrations, and prostate cancer incidence	Bax expression was lower in prostate biopsies in the SPI-group compared to the MPI group after 6 months (P=0.03). There were no differences among treatment groups in total PSA, free PSA, or PSA percent. 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 = 0.013). Prostate cancer incidence was 38 in the MPI group vs. 6% SPI+ group and SPI− group.
Curcumin						
Sharma 2001 [66]	15	Men and women with histiologically-confirmed adenocarcinoma of the colon or rectum refractory to standard chemotherapies. All patients were Caucasian and had undergone previous surgery (United Kingdom)	Subjects were given different doses of a soft gelatin capsules containing 20 mg of curcuminoids. Subjects were assigned to treatments groups 2, 4, 6, 8, or 10 capsules once daily with water.	Until disease progression was established or consent was withdrawn	Lymphocytic total GST activity and leukocytic M_1G levels.	Leukocytic M1G levels were constant within each patient and unaffected by treatment. Radiologically stable disease was demonstrated in five patients for 2–4 months of treatment.
Cruz-Correa 2006 [65]	5	Caucasian men and women with Familial Adenomatous Polyposis patients with previous colectomy, ileorectal anastomosis or ileoanal pull through with	Participants received curcumin 480 mg and	9 months	Number and size of polyps at the end of treatment	Subjects were treated with for a mean of 6 months of therapy. On average, polyp number decreased by 60.4% from baseline (P=0.043) and the mean decrease in polyp size from

First Author Year, Study Name*	Number (n)	Population	Intervention	Duration	End Point	Results
		ileal anal pouch more polyps (United States)	quercetin 20 mg orally 3 times a day			baseline with treatment was 50.9% (P=0.039).

*Study names included if applicable

Table 3

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

First Author Year	Number (n)	Population	Intervention	Duration	End Point	Results
Fish Oil						
Bartoli 1993 [67]	40	Males and females with sporadic adenomatous colorectal polyps (Italy)	Double-blind randomized control trial. Subjects were divided into 4 groups. Three groups were given a 30-day supply of fish oil capsules. Each capsule contained 455 ± 55 mg EPA, 395 ± 55 mg of DHA and 0.3 mg of Tocopherol. The first group received a daily total amount of 2.5 g EPA+DHA, the second group 5.1 g EPA+DHA and the third group 7.7 g EPA+DHA. The placebo group was supplied with olive oil (approximately 7.7 g/day).	30 days	Cell proliferation of the rectal crypt cells.	Total labeled index and the mean labeled index for the high-crypt region was lower after 30 days of treatment in the treatment groups and the effect was more pronounced at higher dosages. The investigators did not report any estimates of statistical significance.
West 2010 [68]	55	Males and females ages 18–74 with familial adenomatous polyposis, with history of colectomy with ileorectal anastomosis (United Kingdom)	Randomized, double-blind, placebo-controlled trial. Subject were randomized to receive two soft-gel capsule containing 500 mg of omega-3 polyunsaturated free fatty acid form eicosapentaenoic acid (EPA)or placebo twice daily for 6 months.	6 months	Number and size of rectal polyps	Subjects taking EPA experienced a 22.4% (95% CI: 5.1–39.6 %) decrease in polyp number compared with placebo (P=0.012). Subjects in the EPA-FFA treatment group experienced a 29.8% overall decrease in polyp size compared with the placebo group (P=0.027). Subjects in the EPA treatment group also experienced a significant decrease in global polyp burden (P=0.011)
Medicinal Mushrooms						
Mitomi 1992 [70]	448	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. The control group was administered mitomycin C intravenously on the day of and the day after surgery, followed by oral 5-fluorouracil (5-FU, 200 mg a day) for over six months. The treatment group also received mitomycin pre and post-surgery followed by Polysaccharide-K (PSK, 3 grams a day) orally for over three years.	Five years	Colorectal tumor recurrence and disease-free survival	Median follow up was four years. The rates of cancer recurrence were lower in the PSK group than in the control group. The three-year disease-free survival curve was 77.2% in the PSK group compared with 67.7% in the control group. (P=0.013). In patients with colon cancer, the disease-free survival curve of the PSK group was significantly better than that of the control group (P=0.0467). The overall three-year survival curve was 85.5% for the PSK group and 79.2% for the control group (p=0.013). In patients with colon cancer, the overall survival curve of the PSK group was significantly better than that of the control group (P=0.043)
Gao 2003 [71]	34	Males and females with histologically-confirmed, advanced-stage cancer (China)	Subjects were given 1800 mg Ganopoly, three times daily orally before meals for 12 weeks.	12 weeks	Immune parameters (cytokines, T-cell subsets, mitotic response to phytohemmaggl utinin (PHA), and	After 12 weeks there was a significant increase in the mean plasma concentrations of interleukin (IL-2), IL-6, and interferon (IFN)-g. Levels of IL-1 and tumor necrosis factor (TNF-a) were significantly decreased

First Author Year	Number (n)	Population	Intervention	Duration	End Point	Results
					natural killer (NK) activity	(P < 0.05). Treatment with Ganopoly in a significant increase in the mean NK activity after 12 weeks (34.5 ± 11.8% vs. 26.6 ± 8.3%).(P < 0.05)
Kodama 2003 [72]	10	Cancer patients (Japan)	Administered maitake D-Fraction.		NK cell activity, numbers of CD4+, CD8+ in peripheral blood, 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]	398	Men and women ages 40–65 years. Subjects had had at least 2 colorectal tumors removed endoscopically within 3 months before recruitment	Subjects were randomized into four groups: regular intake of wheat bran biscuits, regular intake of *L.casei* preparation, regular intake of both wheat bran biscuits and *L.cassei* preparation, and no treatment. All four groups received dietary instructions.	4 years	Colorectal cancer diagnosed by colonoscopy	The administration of L. casei and wheat bran did not result in any differences in the development of new colorectal tumors. Multivariate adjusted ORs for occurrence of tumors 1.31 (95% CI 0.87–1.98) in the wheat bran group and 0.76 (0.50–1.15) in the *L. casei* group compared to the control group. In *L. casei* group there was a lower occurrence rate of tumors with a grade of moderate or severa atypia OR: 0.65 (95% CI: 0.43–0.98).
Klein 2008 [75]	26	Males and females in good general health (mean age 25 years) (Germany)	Placebo controlled, crossover study. Participants were initially randomized into one of two groups. 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 for a period of 5 weeks. The two groups were crossed during the following 5-week period.	5 weeks	Immunological parameters including number of lymphocytes, monocytes, granulocytes, and T-cell expression,	Most immunological parameters did not change significantly following the intervention. Cell counts of lymphocytes, monocytes, granulocytes, and the expression of various CD cells and HLA-DR did not change throughout the study.

Table 4

The American Institute for Cancer Research's Recommendations for Cancer Prevention [79]

1	Be as lean as possible without becoming underweight.
2	Be physically active for at least 30 minutes every day.
3	Avoid sugary drinks. Limit consumption of energy-dense foods.
4	Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans.
5	Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.
6	If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day.
7	Limit consumption of salty foods and foods processed with salt (sodium).
8	Don't use supplements to protect against cancer.
9	*It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids and foods.
10	*After treatment, cancer survivors should follow the recommendations for cancer prevention.

*Special Population Recommendations