Dietary Antioxidants and Human Cancer

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ABSTRACT

Reactive oxygen species (ROS) are by-products of metabolism that increase in the body during inflammation, smoking, and exposure to agents such as radiation and certain drugs. ROS cause damage to DNA and other molecules, and they are implicated in the development and progression of cancer. Antioxidants from endogenous and dietary sources can neutralize and destroy ROS and may play a role in cancer prevention. Experimental and animal studies have shown that treatment with single or combined antioxidants prevents neoplastic transformation of normal cells and inhibits tumor growth. Human observational studies suggest that high intake of antioxidant-rich foods, notably fruits, vegetables, and grains, is inversely related to cancer risk. However, prospective human studies that began to accrue data in the 1990s did not always confirm this relationship. Randomized, controlled clinical trials using specific antioxidant supplementation have also produced mixed results, but study limitations and confounding factors often make it difficult to derive definitive conclusions. Antioxidant supplementation during cancer treatment remains controversial. Radiotherapy and certain chemotherapeutic agents rely on ROS to destroy cancer cells. Although antioxidant supplementation may help protect normal cells from ROS damage and may have palliative effects during cancer treatment, studies suggest that cancer cells may also be protected from ROS damage, thereby reducing treatment efficacy and patient survival. This article reviews evidence for the impact of antioxidant supplementation and antioxidant-rich diets on cancer risk and mortality. It also outlines some of the factors that may have contributed to the conflicting outcomes reported.

Keywords: Antioxidants; Cancer; Diet; Supplements

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INTRODUCTION

Cancer is the second leading cause of death in the United States. The American Cancer Society estimates that in 2017 there will be 1,688,780 new cancer cases and 600,920 cancer deaths.[1] Cancer cells are distinguished by their limitless replicative potential, resistance to growth inhibition, metastatic spread, and evasion of apoptosis. Reactive oxygen species (ROS), which include free radicals and other molecules, are implicated in cancer initiation and progression. On the basis of observational and experimental studies, diets rich in fruits and vegetables have ranked highly as a strategy to lower cancer risk because they contain antioxidants capable of destroying ROS.[1–8] Prospective studies since the 1990s have introduced uncertainty into the perception of the cancer-preventive efficacy of these plant-rich diets. Radiotherapy and certain chemotherapies use ROS to destroy neoplastic cells. Dietary antioxidant supplements such as vitamins C and E have been considered as adjuvants in cancer therapy because they have been shown to mitigate the adverse effects of radiation in some patients. However, they have also been shown to protect cancer cells, thereby reducing treatment efficacy.[9–14]

ANTIOXIDANTS IN CANCER DEVELOPMENT AND TREATMENT

ROS are by-products of normal cellular metabolism, but their levels can increase markedly during inflammation and exposure to certain exogenous factors such as ionizing radiation; nitrogen oxide pollutants; some chemical carcinogens; tobacco smoke; and particular drugs, such as acetaminophen. Antioxidants help defend cells from ROS damage, but a prevalence of ROS over available protective antioxidants results in oxidative stress. Oxidative damage caused by ROS can lead to DNA mutations and altered metabolic pathways that are linked to an increased risk for cancer development.[3–5] Evidence derived from *in vitro* and animal experiments suggests that dietary antioxidants and cellular endogenous molecules with antioxidant capacity can inhibit the growth of neoplastic cells.[4–7] Observational studies have shown that a diet rich in antioxidants reduces the risk of developing certain cancers.[8]

ANTIOXIDANTS DURING CANCER TREATMENT

It is difficult to come to a consensus about the effects of antioxidant supplementation during treatment because of the variability in the studies in which researchers have investigated this question. These include variations in study design, eligibility criteria, intervention protocols, malignancy type, treatment modality, antioxidant form and dose, timing of observation and intervention, and statistical power. It also has to be borne in mind that dietary antioxidants comprise a broad range of chemical classes, including carotenoids, polyphenols, tocopherols, and others that have a wide array of biological activities. Because only a few antioxidants have been used in conjunction with cancer therapeutic agents, it is not possible to make generalizations about how other antioxidant supplements might interact with cancer treatments. In addition, although antioxidant supplements share the ability to quench ROS, their clinical action and potency can vary by type, bioavailability, dose, duration, and route of administration. Any discussion about antioxidant supplementation during cancer treatment must also distinguish between (1) high-dose antioxidant supplementation as an adjuvant therapy with radiation and selected chemotherapy agents and (2) low-dose supplementation of essential antioxidants to support normal functions.

Currently, there is insufficient evidence from well-controlled randomized trials to determine unequivocally whether low-dose antioxidant supplementation taken during treatment for protection of normal cells from ROS damage may provide similar protection to cancer cells and thus diminish treatment effect.[9,10] *In vitro* studies indicate that antioxidants kill tumor cells by apoptosis while sparing normal cells,[11,12] but this has not been replicated in clinical trials. Researchers in a few, often underpowered, randomized controlled trials found that participants who took antioxidant supplements had worse outcomes, especially if they were smokers. In

one study, 540 patients with head and neck cancer received α-tocopherol (400 IU/day) with or without β-carotene (30 mg/day) versus placebo, concurrent with radiation therapy. The median duration of radiation therapy was 43 days, and the median duration of antioxidant supplementation was 3.1 years. During the follow-up (median, 6.5 years), 179 deaths were recorded for the supplement group and 77 for the placebo group. All-cause mortality was significantly increased in patients who had received α-tocopherol alone and those who received β-carotene supplements in addition to α-tocopherol. The addition of β-carotene did not markedly affect the mortality rate.[13] Route of administration may make a difference. A double-blind placebo controlled trial showed that high doses of vitamin C (up to 10 g/day) increased the chemosensitivity of ovarian cancer in mouse models and reduced toxicity in patients with ovarian cancer.[14] Parenteral administration appears more effective than oral administration.[15] Antioxidants may benefit patients after radiation therapy by alleviating adverse side effects. Researchers in one study found that vitamin C (500 mg twice daily) and vitamin E (400 IU twice daily) had palliative effects in patients who had previously been treated with radiation for prostate and gynecologic cancers. A sustained improvement in symptoms was still reported 1 year later.[16]

ANTIOXIDANT FOODS AND CANCER PREVENTION

The potential role of antioxidant-rich fruit and vegetables in helping prevent the onset of diseases, including cancer, has been the subject of basic research and observational and intervention studies.[8,17–27] Observational studies showed that the risk of certain cancers is inversely related to consumption of total fruits and total vegetables that contain essential antioxidant micronutrients and phytochemicals.[8,17,18] The reported results were based mainly on case–control studies, which are notoriously susceptible to recall bias when it comes to reporting on past diet. In the late 1990s, large prospective cohort studies on diet and cancer began to accrue data that did not always confirm the inverse associations reported in the observational studies.

In a large prospective study (the EPIC study), investigators looked at a European cohort of 142,605 men and 335,873 women who developed approximately 30,000 cancers at all sites combined over nearly 9 years of follow-up. The investigators found a weak but statistically significant inverse association – a 4% lower incidence of all cancers combined for an increment of 200 g of total fruits and vegetables per day, which corresponds to about two extra servings per day.[19,20] Regarding the results for specific cancers, analysis of the data showed an inverse relationship between cancers of the upper gastrointestinal tract and fruit intake but not vegetable intake. The risk of colorectal cancer was inversely associated with intake of total fruits and vegetables and total fiber. Lung cancer in smokers was inversely associated with fruit intake but not with vegetable intake. No significant association was found between the intake of total fruits, vegetables, and fiber and observed cancers of the stomach, biliary tract, pancreas, cervix, endometrium, prostate, kidney, bladder, or lymphoma.

A prospective study performed within the NIH-AARP Diet and Health Study showed a different pattern of results. The investigators identified 15,792 cancer cases in 195,229 women and 35,071 cancer cases in 288,109 men, and they estimated relative risks associated with the highest compared with the lowest quintile of fruit and vegetable intakes. The complex results highlight the difficulty in reaching conclusions. Total cancer among women and men was not associated with the intake of fruits or vegetables. However, analysis of risk for cancers at specific sites revealed that men had a lower risk of pancreatic cancer with fruit intake, colorectal cancer and lung cancer with vegetable intake, and an increased risk for prostate and thyroid cancer with vegetable intake. Fruit intake lowered the risk of breast cancer in women, but an intake of vegetables increased breast cancer risk. The conclusion of the investigators based on total cancer was that the results did not support an association between fruits and vegetables and total cancer in men and women.[21]

A particular food component may provide a more selective benefit than others. In a case–control study, the intake of allium vegetables (onions, leeks, garlic) high in organosulfur compounds and other antioxidants selectively reduced gastric cancer.[18] Authors of a systematic review of prospective studies on citrus fruit and cancer found that with

each 100 g/day increased intake of citrus fruits, there was a marginally significant decreased risk of esophageal cancer (six studies), squamous cell carcinoma (three studies), and esophageal adenocarcinoma (three studies). A nonsignificant inverse relationship was found for gastric cardia cancer but not for gastric noncardiac cancer (four studies).[22]

Evidence for fruits and vegetables lowering the risk of hormonally regulated cancers is inconsistent. Nevertheless, some studies have reported a protective effect. In case–control studies of Asian women, green tea, which is rich in antioxidant polyphenols, significantly reduced the risk of breast cancer.[23] The consumption of cooked tomatoes and tomato products, which are rich in the carotenoid lycopene, a powerful antioxidant, was linked to lower incidences of a number of cancers, most strongly prostate cancer.[24]

A weak association between intake of fruits and vegetables and cancer risk may still represent a true protective effect. Even if the evidence for the cancer-preventive effects is not as strong as previously thought, accumulating data support benefits for preventive effects against cardiovascular disease. For example, men and women who showed no inverse relationship between total cancer rates and intake of fruits and vegetables in the EPIC study showed a 30% reduction in the incidence of coronary heart disease or stroke when consuming five or more servings per day, compared with those eating less than 1.5 servings per day.[17] Thus, recommendations to increase the intake of fruits and vegetables have a sound basis.

Differences in the outcomes of studies on the protective effects of antioxidant-rich foods may be due in part to differences in genetics, age, sex, and lifestyle in study participants and differences in the food itself. Fruits and vegetables vary widely in their composition and their antioxidant capability. Antioxidant levels in any particular plant food depend on growing conditions, such as soil composition, moisture, and temperature. Variations in the handling and storage of food after harvest, as well as differences in food preparation methods, also affect antioxidant composition. In addition, several endogenous enzymes that scavenge ROS, such as superoxide dismutase, catalase, and peroxidases, depend on dietary micronutrients for their activity. Copper and zinc act as coenzymes for superoxide dismutase; iron is required for catalase; and selenium, a dietary trace element, is a component of the enzyme glutathione peroxidase that breaks down the ROS peroxide.[5,6,8,24] Thus, any deficiency of these cofactors in study participants, or any depletion in vegetables and fruits used as interventions, might also contribute to the inconsistent findings on the protective effects of antioxidant-rich foods.

ANTIOXIDANT SUPPLEMENTS AND CANCER PREVENTION

Observational studies, including case–control and cohort studies, on the effect of antioxidant supplements in cancer prevention have shown mixed results but are on the whole supportive.[28] Because observational studies cannot control for a variety of biases that may influence outcome, each study must be critically evaluated.

By contrast, randomized, controlled clinical trials lack most of the limiting biases encountered in observational studies. Such intervention studies are considered more reliable evidence of benefits or harm. Randomized controlled trials on the role of dietary antioxidant supplements in cancer prevention have looked at a small number of essential dietary antioxidants, including β-carotene, vitamin A, vitamin E, vitamin C, and selenium, given mostly in large doses and lasting relatively short periods of time. Fraught by limitations in the studies, results have been mixed. The researchers in the randomized controlled trials described below investigated the ability of specific dietary antioxidant supplements, given in single or combined form, to lower cancer risk and/or mortality.

The Linxian Nutrition Intervention Trial was the first large-scale randomized trial to investigate whether dietary supplementation with specific vitamins and minerals lowered mortality from cancer. The people of Linxian County, China, have one of the world's highest rates of esophageal and gastric cancer and a low intake of micronutrients. Chinese men and women at risk of developing esophageal and gastric cancer were randomly assigned to take a variety of combinations of antioxidants that ranged from one to double the recommended daily dose.[29] One regimen was the combination of a daily dose of 15 mg of β-carotene, 30 mg (33.3 IU)

of vitamin E, 50 μg of selenium, or no antioxidant supplementation over 5 years. Initial results showed that participants who took the supplements lowered their risk of death by gastric cancer but not by esophageal cancer.[29] A 10-year follow-up showed that the lowered risk of death from gastric cancer was no longer present in those who took the antioxidants.[30]

The researchers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC), which was done in Finland, investigated whether daily intake of vitamin E (α-tocopherol) and β-carotene over 5–8 years would lower lung cancer incidence in male smokers. The results showed that β-carotene at 20 mg/day *increased* the incidence of lung cancer. Vitamin E at 50 mg (55.5 IU) per day reduced the incidence of prostate cancer by 34%, but a follow-up study showed that this reduction was substantially attenuated within the first 3 years after the trial, following cessation of supplementation.[31]

The researchers in the Carotene and Retinol Efficacy Trial (CARET) investigated the effect of daily β-carotene (30 mg) and retinyl palmitate (25,000 IU) on the incidence of lung cancer and other cancers, as well as on death, in participants who were at high risk for lung cancer because of a history of smoking or asbestos exposure. CARET began in 1986 and was stopped ahead of schedule in January 1996 because participants who were randomly assigned to receive the intervention showed a 28% increase in incidence of lung cancer, a 17% increase in incidence of death, and a higher rate of cardiovascular disease mortality than participants in the placebo group.[32] A report in 2004 showed that the adverse effects persisted for up to 6 years after stopping supplementation, though the increased risk of lung cancer and all-cause mortality observed earlier were no longer statistically significant compared with placebo.[33]

The investigators in the Physicians' Health Study-I examined the effects of β-carotene at 50 mg every other day for 12 years on cancer mortality or all-cause mortality in healthy male physicians. The results reported in 1996 showed no effects in smokers and nonsmokers.[34] These results differ from the CARET and ATCB trials, where cancer incidence was higher in smokers taking β-carotene,[33,35] and no clear explanation is provided.[34]

The researchers in the Physicians' Health Study-II investigated whether 400 IU of vitamin E taken every other day, 500 mg of vitamin C taken every day, or a combination of both would have an effect on cancer incidence in healthy male physicians aged 50 years and older. The study was carried out over 7.6 years, and the results, reported in 2009, showed that supplementation with either antioxidant or both did not reduce cancer incidence.[36]

The investigators in the Women's Health Study examined the effects of β-carotene (50 mg every other day), vitamin E (600 IU every other day), and aspirin (100 mg every other day) on cancer incidence and cardiovascular disease in U.S. women aged 45 years and older. The results, reported in 1999, showed no benefit or harm associated with supplementation.[37] A report in 2005 showed similar results for vitamin E.[38]

The role of selenium in cancer prevention has been of interest for some time. Experimental studies have shown selenium to have protective effects, and it is known that regions low in selenium have higher rates of cancer.[6] A large multicenter clinical trial showed that subjects with a history of skin cancer who were supplemented with 200 μg of selenium for a mean of 4.5 years (SD, 2.8 years) had a significant reduction in lung, prostate, and colorectal cancer but not skin cancer, suggesting that selenium could not reduce the risk of skin cancer recurrence.[39] A subsequent randomized controlled trial by the same investigators looked at the effects of selenium in men who were at high risk for prostate cancer. Participants were randomized to receive a daily oral dose of 200 μg or 400 μg of selenium or placebo. They were observed for 5 years with follow-up every 6 months. Selenium supplementation was shown to have no effect on the incidence of prostate cancer in this population.[40] The authors concluded that this and other studies indicate that selenium supplementation may not have a role in preventing prostate cancer.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was the result of what appeared to be growing evidence at the time that selenium and vitamin E may reduce the risk of prostate cancer.[41,42] SELECT was a large, randomized, controlled phase III trial in which researchers investigated whether daily supplementation with 200 μg of selenium, 400 IU of vitamin E (α-tocopherol), or both would

lower the incidence of prostate cancer in men aged 50 years or older.[43] The study began in 2001 and was terminated in 2008, 5 years earlier than originally planned. The results showed that intake of these supplements over 5.5 years did not reduce the incidence of prostate cancer or other cancers. An update reported in 2011 revealed that after an average of 7 years (5.5 years on the supplements and 1.5 years off), there were 17 percent more cases of prostate cancer in men taking vitamin E alone than among men on placebo. There was no increase in prostate cancer among men who were assigned to take selenium alone or vitamin E plus selenium, compared with men assigned to take placebo.[44]

In the SU.VI.MAX study, the impact of sex was observed in a randomized, placebo-controlled trial conducted in France with 7876 women aged 35–60 and 3560 men aged 45–60 years. The researchers investigated the potential cancer-preventive effects of low-dose vitamin C, β-carotene, vitamin E, selenium, and zinc. After 7.5 years, low-dose antioxidant supplementation was associated with a reduced total cancer incidence and all-cause mortality in men but not in women. It was thought that supplementation may have been effective only in men because of their lower baseline status of certain antioxidants, especially β-carotene.[45]

DIETARY ANTIOXIDANTS: CONFRONTING THE DILEMMA

Antioxidants, including endogenous enzymes, other molecules such as glutathione, and dietary nutrients, contribute to the body's defense systems. Antioxidants neutralize and remove ROS, including free radicals that damage DNA and other molecules, inducing mutations that may lead to cancer. Dietary antioxidants also maintain the body's metabolic and structural health. Vitamin C, for example, plays a role in collagen synthesis.

Antioxidants in plant foods are complex mixtures of vitamins, minerals, and phytochemicals that may cooperate with one another in additive or synergistic ways, thereby augmenting antioxidant activity. In some studies, this may partly account for the lack of benefits found in reducing cancer risk by supplements that are purified chemicals given in doses higher than the amounts present in food. The main essential micronutrients for antioxidant activity are lipid-soluble vitamin A, with low antioxidant activity, converted from the powerful antioxidant phytochemical β-carotene; lipid-soluble vitamin E, largely in the form of α-tocopherol; and water-soluble vitamin C (ascorbic acid). Several minerals have antioxidant activity by virtue of being part of antioxidant enzymes. These include selenium, zinc, manganese, magnesium, iron, and copper. Nonessential antioxidants in plant foods include lycopene (a carotenoid), polyphenols, and flavonoids.

Some dietary antioxidants display a double-edged sword.[46] For example, β-carotene at low doses acts as an antioxidant with anti-inflammatory properties, but at high doses it has pro-oxidant actions that produce proinflammatory mediators such as tumor necrosis factor-α. Free radicals produced in smoking are thought to play a role in the increased cancer risk observed in smokers receiving β-carotene. *In vitro* studies show that vitamin C at high doses is a pro-oxidant and has a cytotoxic effect on cells by generating hydrogen peroxide.[15] Antioxidant supplements used in randomized trials may have had detrimental metabolic effects independent of their antioxidant actions, which may have affected study outcomes. In addition, megadoses of dietary antioxidants have also generally failed to prevent human disease, in part because they do not decrease oxidative damage as indicated by biomarkers for inflammation.[5]

DISCUSSION

Cancer is a complex, multistage disease that entails genetic mutations and epigenetic events. Although many of the factors involved in cancer development are unknown, ROS, including free radicals, are thought to play a role. ROS are formed naturally during cellular metabolism and increase during inflammation and exposure to environmental agents, including tobacco and ionizing radiation. At high concentrations, ROS can damage DNA, cell proteins, and cell membranes. Damage particularly to DNA, which induces mutations, may initiate cancer and contribute to its progression.[2–5] Endogenous and dietary antioxidants scavenge and neutralize ROS, potentially preventing any cancer-causing effects. Supportive evidence for the role of antioxidants in cancer prevention came from experimental studies and from epidemiologic studies which

showed that a high intake of fruits and vegetables rich in antioxidants reduced the risk of certain cancers.[6,8,17,28] Some more recent prospective studies have challenged these observations.[19,20]

Support for dietary intake of antioxidants in lowering cancer risk originally came from observations about the protective effects of the Mediterranean diet, which is rich in antioxidant-containing fruits, vegetables, grains, and olive oil. Adherence to the diet was associated with a reduced risk of overall cancer mortality as well as a lower incidence of colorectal, breast, gastric, prostate, liver, and head and neck cancers. When the various components in this diet were assessed for their contribution, no single ingredient or specific food category was found to mediate the beneficial effects, suggesting that they were the result of complex interactions.[47] A systematic review by the U.S. Preventive Services Task Force of available evidence on the use of antioxidant vitamins and mineral supplements for preventing chronic diseases, including cancer, did not produce unequivocal evidence for benefit in cancer prevention.[48]

Researchers in randomized controlled trials have examined a variety of antioxidant supplements for their impact on cancer risk or mortality. In most cases, the trials showed that isolated dietary antioxidant supplements (vitamins A, E, and C; β-carotene; and selenium), given singly or in combination, often at doses twice as high as government recommendations, did not reduce cancer risk or mortality. In some studies, β-carotene supplementation appeared to increase lung cancer risk in smokers.[32]

The role of antioxidants in cancer treatment remains unclear. Many patients with cancer take dietary supplements, particularly antioxidants, to reduce the toxicity associated with cancer treatment. Despite more than two decades of research, evidence for the safety and efficacy of concurrent use of dietary antioxidants during cancer treatment remains inconclusive. Some data suggest that antioxidants protect both cancer cells and healthy cells from oxidative damage. Other data suggest that antioxidants can protect normal tissue without interfering with the efficacy of chemotherapy or radiation. Several randomized trials have shown that antioxidants may help as palliative agents and may reduce the toxic side effects of cancer treatment.

The inconsistent outcomes of trials may be due to many factors that relate to study design. These include the chemical form of the antioxidant used, intervention dose, mode of administration, and study duration. In addition, baseline antioxidant status, genetic polymorphisms, gene–nutrient interactions, age, sex, type of malignancy, and health status are potential variables among study participants that are generally unaccounted for and are likely to influence results.[46] Dietary antioxidants also have the potential to interact with one another in their metabolic functions.[49,50] which may limit the effectiveness of selected antioxidant supplements given in single or combined form in pharmacologic doses.

Additional well-designed, randomized, controlled clinical trials that take into account a range of potentially confounding variables are needed to further investigate the role of dietary antioxidants in cancer risk and prevention and to help better define the role that antioxidant supplements may have as adjuvants in cancer treatment. On the basis of current available information, intake of antioxidant-rich fruits and vegetables is encouraged for health maintenance and for its possible role in lowering disease risk.

COMPETING INTERESTS

The author declares she has no competing interests.

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