

Dietary Antioxidants and Human Cancer

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Epidemiological studies show that a high intake of antioxidant-rich foods is inversely related to cancer risk. While animal and cell cultures confirm the anticancer effects of antioxidants, intervention trials to determine their ability to reduce cancer risk have been inconclusive, although selenium and vitamin E reduced the risk of some forms of cancer, including prostate and colon cancer, and carotenoids have been shown to help reduce breast cancer risk. Cancer treatment by radiation and anticancer drugs reduces inherent antioxidants and induces oxidative stress, which increases with disease progression. Vitamins E and C have been shown to ameliorate adverse side effects associated with free radical damage to normal cells in cancer therapy, such as mucositis and fibrosis, and to reduce the recurrence of breast cancer. While clinical studies on the effect of antioxidants in modulating cancer treatment are limited in number and size, experimental studies show that antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread, suggesting a potential role for antioxidants as adjuvants in cancer therapy.

Keywords: diet; antioxidants; cancer; chemoprevention; therapy

Cancer is the second leading cause of death in the United States; the American Cancer Society estimates 1,368,030 newly diagnosed cases in 2004 and 5,637,000 deaths from the disease. While rates vary widely with cancer type and stage in diagnosis, the relative survival rate for all cancers combined is estimated at 63%.¹

Among the possible causes of cancer, damage to DNA and other cellular molecules, by reactive oxygen species, ranks high as a major culprit in the onset and development of the disease. These by-products of normal metabolism, which increase in inflammation and in exposure to exogenous sources including nitrogen oxide pollutants, smoking, certain drugs (eg, acetaminophen, bleomycin), and radiation, can induce cancer-causing mutations, oxidize lipids and proteins, and alter signal transduction pathways that enhance cancer risk.²⁻⁴

Experimental studies support the role of reactive oxygen species in cancer, in part by showing that dietary antioxidants (eg, vitamin E, vitamin C, sele-

nium, β -carotene, and other phytochemicals) as well as endogenous antioxidants (eg, glutathione) that neutralize or trap reactive oxygen species act as cancer preventive agents.^{4,5} Human observational studies provide further support, showing, on one hand, that oxidant stress increases with clinical progression of breast cancer⁶ and, on the other hand, that a diet rich in antioxidant-containing foods reduces the risk of certain cancers.⁷

Once cancer has occurred, however, treatment with radiation and chemotherapeutic agents that generate free radicals in cells largely relies on their oxidative damage to eradicate the cancerous cells.⁸ Thus, the question arises whether antioxidants that protect normal cells from acute and long-term free radical damage⁵ may afford the same protection to tumor cells and hinder the overall outcome of cancer therapy.⁹

Clinicians treating cancer patients are faced with this conundrum, and while rarely restricting the intake of antioxidant-rich food, they may advise patients to refrain from taking antioxidant supplements, lest they interfere with the course of treatment.

New data, however, show that some dietary antioxidants may have potential as adjuvants in cancer therapy by their ability to induce programmed cell death (apoptosis).¹⁰ Studies in cell cultures show that vitamin E, vitamin C, selenium, and some phytochemicals selectively induce apoptosis in cancer cells while sparing normal cells¹¹⁻¹³; other findings, in a model of metastatic growth, show that vitamin C is an angiostatic factor and may have potential in aiding host resistance to tumor growth and invasiveness.¹⁴ Antioxidants also show promise in cancer therapy by their palliative action, reducing painful side effects associated with treatment.¹⁵

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Table 1. Principal Antioxidants and Their Interactions

<i>Antioxidant</i>	<i>Interaction</i>
Vitamin C	Regenerates active α -tocopherol (vitamin E) by reducing its radical form
Vitamin E	Transport and storage depend on selenium; absorption is reduced when vitamin A and β -carotene levels are high
β -carotene	Conversion to vitamin A requires vitamin E
Selenium	Synergistic with vitamin E

Data from Borek.⁴

Diet in Cancer Prevention

Protecting normal cells from events that may trigger or promote cancer is a primary goal in maintaining health; it also serves to prevent long-term damage that may occur during cancer therapy and give rise to secondary malignancies in later years.⁸ Epidemiological data from more than 250 case control and cohort studies show that the risk of certain cancers is inversely related to the consumption of vegetables and fruit that contain essential antioxidant micronutrients, numerous other essential micronutrients, phytochemicals, and fiber.¹⁶ While inverse risk is seen for cancers of the mouth and pharynx, esophagus, lung, stomach, colon, and rectum, the data for hormonally regulated cancers, including breast and prostate cancer, are not consistent. Reduction in breast cancer risk was often associated with consumption of carrots and green vegetables that are rich in carotenoids, and a reduced prostate cancer risk was seen with intake of cruciferous vegetables, yellow vegetables, and tomatoes that are rich in lycopene. Intake of allium vegetables (garlic, onions) that contain high levels of antioxidant organosulfur compounds is associated with reduced gastrointestinal cancer risk^{16,17}; green tea, which is rich in polyphenols, has been shown to significantly reduce the risk of breast cancer and ovarian cancer in Asian women.^{18,19}

Antioxidant Micronutrients

Although it is hard to ferret out with assurance the cancer-preventive compounds in fruits and vegetables, the major nutritional antioxidants, which cooperate closely with one another (see Table 1), are deemed to have a major protective role against the disease. Animal and cell culture studies show that vitamin E, vitamin C, β -carotene (pro-vitamin A), and the mineral selenium prevent transformation of normal cells to cancer cells.^{4,5,16} In view of the suggested protective effects of antioxidants seen in observational studies, 5 large intervention trials were carried out in the 1990s to evaluate the cancer-preventive effects of a variety of micronutrients: in a study in China on the effects of vitamin E, vitamin A, and β -carotene in vari-

ous combinations and on lung cancer risk in smokers in the United States and Finland.^{16,20}

While combined treatments with selenium (50 μ g), β -carotene (15 mg), and vitamin E (α -tocopherol, 30 mg) resulted in a lower incidence of cancer and a 10% reduction in cancer mortality from esophageal and gastric cancer in the China study; vitamin A and β -carotene as well as α -tocopherol did not reduce lung cancer risk in smokers. Vitamin E, however, significantly reduced the risk of prostate cancer by 32% and reduced mortality from colorectal cancer.^{16,20}

Since the results of these intervention trials were reported, new studies have addressed the role of vitamin E, β -carotene, and selenium in reducing cancer risk.²¹⁻²⁴ A landmark multicenter clinical trial by Clark and colleagues²⁴ showed that subjects with a history of skin cancer who were supplemented with 200 μ g of selenium for a mean of 4.5 years (SD = 2.8 years) had a significant reduction in total cancer (all sites combined) and lung, prostate, and colorectal cancer (though not skin cancer), indicating that once skin cancer had occurred, selenium could not reduce the risk of recurrence.

In a study designed to test the association between levels of tocopherols (α and γ) and selenium and subsequent prostate cancer,²¹ investigators found a decline in prostate cancer with increasing concentration of α -tocopherol, and a 5-fold reduction in the risk of developing prostate cancer with increased levels of γ -tocopherol. Selenium showed protection, and supplementation with high levels of selenium and α -tocopherol was associated with a significant decrease in prostate cancer only when γ -tocopherol concentrations were high, suggesting a more important role for γ -tocopherol than previously considered.²¹ Selenium alone has been shown to reduce the risk of prostate cancer²² and lung cancer.^{23,24} The growing evidence that selenium and vitamin E may reduce prostate cancer risk has led to the design of the Selenium and Vitamin E Cancer Prevention Trial (SELECT), an ongoing large-scale randomized and controlled phase III trial, to investigate further the role of selenium and vitamin E in prostate cancer prevention. Enrollment began in 2001, with final results anticipated in 2013.²⁵

β -carotene, which had no chemopreventive effects on lung cancer in smokers,²⁰ showed promise in a study on breast cancer. A nested case-control study investigated the association between serum and plasma concentration of retinol, retinyl palmitate, α - and β -carotene, β -cryptoxanthin, lutein, lycopene, and α - and γ -tocopherol and subsequent development of breast cancer. The results showed about a 50% reduction in breast cancer risk in women with high levels of β -carotene, lycopene, and total carotene compared to those with a low level of these micronutrients.²⁶

Antioxidants in Cancer Therapy

While the efficacy of antioxidants during cancer treatment is still being evaluated and clinical trials are ongoing or being set up,²⁷ many cancer patients who are undergoing therapy take antioxidant supplements in an effort to alleviate treatment toxicity and improve long-term outcome.

The modulating effects of antioxidants in treatment depend on a wide range of factors, including the metabolic state of the patient, the stage and site of the disease, and the modality being used. In contrast to radiation treatment, which interacts with the target tissue within a fraction of a second and is gone, producing damage at the time of treatment, agents used in chemotherapy are not confined to the target tissue; they prevail in the body for some time and can interact with and damage a plethora of cellular molecules at different sites for longer periods of time, depending on metabolism, increasing lipid peroxidation of molecules, reducing antioxidant levels, and enhancing oxidative stress.^{28,29}

The primary focus of radiation therapy and chemotherapy is to produce irreversible DNA damage in tumor cells that will prevent their replication and lead to their demise. Another course of action is to alter cellular homeostasis and modify signal transduction pathways, redox state, and disposition to apoptosis. The cellular changes would, ideally, enhance tumor cell killing, largely by apoptosis, and reduce the probability of normal cell death.

Radiation Therapy and Chemotherapy

Anticancer Drugs

Almost all anticancer drugs work by affecting DNA synthesis; they do not kill resting cells unless those cells divide soon after exposure to the drug. Consequently, the efficacy of anticancer drugs used in chemotherapy is limited by the fraction of actively dividing cells. Most anticancer drugs do not rely on reactive oxygen species, although a few produce free radicals that play a role in treatment; these include bleomycin, which produces superoxide radicals; doxorubicin (Adriamycin); and cisplatin, but although bleomycin is more toxic to oxygenated cells, similar to x-rays and γ -rays, doxorubicin is preferentially toxic to hypoxic cells. The potential effect of antioxidants in modifying treatment efficacy would depend on the type of drug in use. Antioxidant protection of normal cells, however, would occur, in principle, in all treatments, even when the mechanism of the chemotherapeutic drug is independent of free radical action; antioxidants help maintain the health of normal tissues and protect them from the toxic effects of free radical-producing

cytokines that circulate in cancer patients and increase with the severity of the disease.³⁰

Radiation Therapy

Radiotherapy uses mostly x-rays and γ -rays (electromagnetic radiation) and to a lesser extent heavy particle radiation, such as protons and neutrons. Radiation may be classified as directly or indirectly ionizing. When any form of radiation is absorbed in tissues, there is a possibility that it may interact directly with cellular targets. In the direct action, which is dominant when neutrons or protons are considered, the atoms of the target, such as DNA, are directly ionized or excited, initiating events that lead to biological changes. Alternatively, radiation may damage cells by indirect action; in this mode of action, which is dominant in treatment with x-rays and γ -rays, radiation interacts with cellular atoms or molecules (mainly water, which comprises 70% of the cell) to produce free radicals, such as superoxide and hydroxyl radicals (the most toxic) that diffuse far enough to reach and damage critical targets, such as DNA. The free radicals form a wide range of other highly toxic reactive oxygen species, such as hydrogen peroxide and peroxy-nitrite, which is produced by the interaction of nitric oxide (NO) and superoxide.

About two thirds of x-ray and γ -ray damage is caused by free radicals^{8,9} that kill tumor cells but threaten the integrity and survival of surrounding normal cells.

Radiation induces mitotic cell death in dividing cells and activates pathways that lead to death by apoptosis in interphase cells and differentiated cells. Response to radiation depends on the type and dose of radiation, inherent tissue sensitivity, and intracellular factors that include position in the cell cycle, oxygen concentration, and levels of thiols and other antioxidants. In the cases of treatment with x-rays or γ -rays (indirect action), the extent of DNA damage depends on intracellular oxygen that must be present during radiation, or at least during the lifetime of the free radical (10^{-5} s).

Oxygen binds to short-lived free radical sites in DNA (a process of oxidation) and “fixes” (ie, makes permanent) the damage produced by free radicals. In the absence of oxygen, damage produced by the indirect action may be repaired. Oxygen modifies the indirect but not the direct action of radiation. Antioxidants compete with oxygen binding and oxidation, chemically reducing the free radicals and repairing the damage, a factor that helps maintain normal cells’ integrity and affects tumor cells to a lesser extent; tumor cells are exposed, in a targeted way that considers cell cycle variations and growth patterns, to high doses of radiation and to hypoxic cell sensitizers that mimic the oxygen effect.⁸

Cancer Treatment Reduces Tissue Antioxidants

The development of cancer produces oxidative stress that increases with disease progression^{6,9,28}; levels of antioxidants further decrease in response to treatment,^{6,9,29} and therapeutic doses of radiation deplete α -tocopherol in normal cells, increasing their risk of damage.^{3,4} A decline in tissue vitamin E and selenium, during radiation therapy of breast cancer, and a marked reduction in vitamins A, C, E, β -carotene, and selenium during breast cancer treatment with doxorubicin, would increase normal tissue sensitivity to free radical damage during radiotherapy and treatment with anticancer drugs.

Age-Related Antioxidant Radioprotection

Age plays a modifying role in treatment response. Endogenous antioxidants decrease with age, as does DNA repair capacity; exposure to radiation and to anticancer drugs that produce free radicals further decreases cellular and blood levels of antioxidants. Human plasma proteins, which contain sulfhydryl moieties and dietary antioxidants such as vitamins C and E and selenium, are radioprotective. Studies of people 30 to 80 years old found an inverse relationship between age and plasma radioprotection, suggesting that an increased antioxidant intake with age would help halt oxidative damage by radiation.³¹

Antioxidants and Tissue Specificity in Therapy

Antioxidant efficacy in tissues depends on the prevailing oxygen partial pressure (PO_2) and the nature of the antioxidant, a point that should be considered in antioxidant supplementation during therapy. β -carotene is an effective chain-breaking antioxidant at low oxygen pressure and less efficient at high oxygen pressure, where it may even act as a prooxidant; this may partly explain the lack of efficacy in reducing lung cancer risk in smokers.²⁰ By contrast, α -tocopherol is an efficient antioxidant in cells with a high oxygen pressure, for example, the lung. The radiation oncologist aims to increase the oxygen content of tumors to enhance the efficacy of cell killing; as PO_2 differs among tumors, so would the modulating effect of antioxidants in radiation therapy, varying with antioxidant used and the tumor PO_2 .³²

Antioxidants and Apoptosis

Selenium

The micronutrient selenium has antioxidant action by virtue of its being an integral part of glutathione peroxidase, which destroys peroxides. While its activity in

normal cells results in the inhibition of transformation by radiation, in part by increasing inherent levels of antioxidants and doubling the breakdown of peroxide⁵ and in stimulating DNA repair in cells with functional p53 (normal cells), selenium does not modify antioxidant levels in some cancer cells (eg, leukemia; C. Borek, unpublished data), which would potentially help eradicate the tumor by treatment modalities that rely on free radical damage.

The apoptotic effects of selenium on cancer cells have been seen largely in cell cultures. Selenium induces apoptosis in prostate cancer cells and protected normal human fibroblasts but not squamous cell carcinoma cells, from single and multiple doses of radiation³³; methylselenocysteine has been shown to block the expansion of premalignant lesions in the mammary gland and to induce apoptosis in human breast cancer cells.³⁴ Selenium may have potential in helping overcome the development of drug resistance in cancer cells, one of the serious problems in chemotherapy; a recent report shows that treatment of doxorubicin-resistant human small-cell lung carcinoma cells with selenium resulted in massive apoptosis, while treatment of the parental doxorubicin-sensitive cells resulted in necrosis.³⁵

Vitamin E, Vitamin C

As a cancer-preventive agent, vitamin E acts in synergy with selenium, preventing cell transformation by x-irradiation, suggesting its use in protecting normal cells against the potential late effects of secondary cancers following radiotherapy.^{5,9} Vitamin E has been found to selectively act as an anticancer drug, alone or in combination with chemotherapy and radiation.

Vitamin E (α -tocopherol succinate), given alone or in combination with γ -rays, selectively induced mitotic accumulation in human cancer cells compared with normal fibroblasts and had a growth inhibitory effect on a variety of cancer cells.³⁶ A combined treatment with vitamins E and C inhibited apoptosis in human endothelial cells more effectively than each alone, while upregulating the antiapoptotic protein Bcl-2 and downregulating the proapoptotic Bax.³⁷ By contrast, vitamin E induced apoptosis in human breast and prostate cancer cells as well as leukemia¹¹ and glioblastoma cells.¹²

In animal studies, vitamin E (tocopherol), given by injection or orally in acetate form, at 50-mg/kg body weight 7 days before tumor irradiation, significantly increased the radiation-induced growth retardation of rat sarcoma. A higher dose of 1 g/kg body weight neither sensitized nor protected the tumor,³⁸ pointing to the potential complexity of the effects of vitamin E in vivo in modifying tumor response to treatment modalities.

Vitamin E succinate has been shown to inhibit colon cancer cell growth and to reduce the number of liver metastases in mice with colon cancer, in some cases by 75%. Vitamin E promoted tumor cell apoptosis and inhibited cell proliferation in vivo.³⁹

One of the clinical problems in treatment of melanoma is relapse of the cancer after surgical treatment. Vitamin E shows promise in helping prevent relapse. Animal studies show that vitamin E succinate promoted melanoma dormancy, reduced the expression of vascular endothelial growth factor, which plays a role in tumor angiogenesis, and inhibited angiogenesis in the melanoma, thus reducing the risk of tumor growth and invasiveness.⁴⁰

A case-control study on diet and breast cancer showed a similar protection by vitamin E and vitamin C against a recurrence of disease. The most imminent fear for women who are successfully treated for their primary breast cancer is a recurrence; 5-year risk of relapse is between 10% and 20%. A recent study shows that, overall, the intake of antioxidant vitamin supplements was associated with a lower risk of breast cancer recurrence and mortality; use of vitamin E (10-40 and more than 40 mg/d) and C (60-500 and more than 500 mg/d) showed an inverse association.⁴¹ Consumption of either vitamin C or E for 4 or more years, starting before diagnosis, showed a strong and significant reduction in risk (odds ratio [OR] = 0.30); when consumed solely after diagnosis, vitamin E slightly reduced risk of recurrence and mortality (OR = 0.75%), while vitamin C did not show a protective effect (OR = 0.90). The data suggest that increasing the length of use of antioxidants is associated with risk reduction for breast cancer recurrence.

Clinical trials to determine the potential use of vitamin E in augmenting the effects of radiotherapy and chemotherapy on diverse cancers are few and small.⁴² A phase II trial was conducted in 45 patients with advanced head and neck squamous cell carcinoma in which α -tocopherol was given with cis-retinoic acid and interferon- α , after treatment with surgery, radiotherapy, or both. There was an 84% disease-free survival at 2 years, although it is difficult to determine the contribution of vitamin E to other anticancer therapy in the absence of controls. The investigators of the trial are now conducting a placebo-controlled phase III study.

Vitamin E, Neurons, and Glioblastoma

Brain tissue is highly sensitive to free radical damage because of its low level of endogenous antioxidants, notably vitamin E and superoxide dismutase. In addition, aging neuronal mitochondria are prone to oxidative damage. Vitamin E protects the integrity of normal neurons and prevents toxicity and apoptosis by

amyloid β peptides, which increase in the brain with age and in dementia and produce free radicals.⁴³

By contrast, vitamin E induces apoptosis in cells derived from glioblastoma multiforme, the most common and aggressive human brain cancer, which resists all forms of therapy. Vitamin E (α -tocopherol succinate) induces apoptosis in a dose-related manner; a 48-hour exposure with 50 μ mol α -tocopherol succinate results in a 15% increase in apoptosis in the glioblastoma cells over controls.¹² Pretreatment with vitamin E may therefore have potential in sensitizing glioblastomas to radiotherapy.

Preventing Therapy-Induced Injury

While antioxidant vitamins E, C, and selenium may have potential in enhancing the efficacy of cancer treatment by radiotherapy and chemotherapy, they may also protect against side effects to normal tissues that are associated with treatment.

Vitamin E (400 IU) and vitamin C (500 mg) protect against proctitis, a painful chronic injury that affects 5% to 20% of patients receiving radiotherapy for cervical and prostate cancer¹⁵; a clinical trial that combined radiation treatment of head and neck cancer with vitamin E (1000 IU/d) and pentoxifylline (800 mg/d) supplementation showed a striking regression of chronic radiation-induced fibrosis, a complication associated with radiation therapy that is difficult to manage clinically, as it does not regress spontaneously.⁴⁴ A combination of vitamin E and pentoxifylline also reduced fibroathrotic uterine lesions in young women who had been previously irradiated for childhood cancer, with 20 to 40 Gy, in treatment that included the pelvic area.⁴⁵

Several clinical studies have tested the efficacy of antioxidants in ameliorating toxic side effects in chemotherapy, which are of major concern in patients treated for solid tumors. Cisplatin is currently the most important cytostatic agent for treating a wide range of solid tumors and palliative in metastatic cancers.⁴⁶ Cisplatin is a free radical-producing drug that significantly decreases plasma concentration of antioxidants.²⁹ Nephrotoxicity, loss of high tone of hearing, and peripheral neuropathy are major long-term side effects in cisplatin treatment. These toxic effects, which are in part irreversible, are largely attributed to free radical damage, reduction in antioxidant levels, and oxidant stress, which are induced by cisplatin.⁴⁶ Formation of free radicals leading to oxidant stress has been shown to be the major pathogenic mechanism in the toxic side effects of cardiomyopathy in doxorubicin therapy and pulmonary damage in bleomycin treatment.⁴⁷

A recent randomized, placebo-controlled, double-blind study tested the effects of supplementation vita-

min E (dl- α -tocopherol acetate 400 mg), vitamin C (ascorbic acid 1000 mg), and selenium (100 μ g) compared to placebo in patients with solid tumors treated with cisplatin.⁴⁶ While there were no significant differences in nephrotoxicity and ototoxicity between supplemented patients and placebo over 12 months of chemotherapy that markedly reduced antioxidant levels, patients who achieved the highest plasma concentrations of these 3 antioxidants, including those who had a higher antioxidant status from the start, had a significantly smaller loss of high-tone hearing. As vitamin E has shown protection against cisplatin-induced neurotoxicity in another study, the present results are attributed to poor compliance and/or inadequate supplementation, promoting the initiation of a new study with vitamins E, C, selenium, and 8 other antioxidants.⁴⁶

Other studies have shown that vitamin E (total of 800 mg/d) prevents oral mucositis in doxorubicin-treated patients, in some cases with complete resolution,⁴⁸ and helps attenuate cardiomyopathy in cancer patients treated with doxorubicin and/or radiotherapy.⁴⁹

Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 (CoQ10) is a cellular protective lipid that has a vital role in energy production as an electron carrier in the respiratory chain.⁵⁰ CoQ10 is also a potent antioxidant and maintains the antioxidant state of vitamin E. CoQ10 is synthesized in human cells under the control of HMG CoA reductase, an enzymatic pathway it shares with cholesterol; thus, patients taking cholesterol-reducing statin drugs may be advised to take CoQ10, whose synthesis is decreased during statin treatment. Synthesis of CoQ10 decreases with aging⁵⁰; as cancer is an age-related disease, oxidative stress, which occurs during the disease and is compounded in older persons, is further enhanced following radiation or anticancer drug treatment, thereby depleting critical levels of CoQ10 that are needed in energy production and antioxidant protection.⁵⁰

A potential important role for CoQ10 during chemotherapy is the prevention of doxorubicin-induced cytotoxicity, with several studies showing that CoQ10 supplementation may provide a safe and effective way to reduce or prevent cardiotoxicity associated with chronic treatment with anthracyclines.⁵¹

Phytochemicals

In addition to the more common nutrient antioxidants, a wide range of phytochemicals, including flavonoids, carotenoids, and organosulfur compounds, are antioxidants and prevent free radical damage by radiation and some chemotherapeutic agents in experimental systems.⁴ These phytochemi-

als induce apoptosis in cancer cells; they may have a potential role in adjuvant cancer therapy and may protect normal cells from the acute and long-term effects of free radicals produced in the course of treatment.

Garlic

Garlic contains radioprotective antioxidants that are amplified in aged garlic extract (Kyolic), an odorless supplement made from organic garlic by a process of extraction and aging.⁵² Aged garlic extract is richer in antioxidants and is more effective in boosting immunity compared to fresh garlic⁵³; its main antioxidant is the water-soluble S-allyl cysteine, which is highly effective in protecting cells from oxidant damage by radiation and anticancer drugs.¹⁷

Recent studies suggest that aged garlic extract that has cancer-preventive effects may have a potential role as an adjuvant in cancer therapy; the water-soluble organosulfur compound S-allyl mercaptocysteine, which is unique to aged garlic extract, induces apoptosis in human prostate, breast, and colon cancer cells as well as leukemia cells.⁵⁴ S-allyl mercaptocysteine activates caspase 3, the executioner enzyme in apoptosis, inhibits antiapoptotic protein Bcl-2, and disrupts microtubules in the cancer cells, preventing further growth.⁵⁵

In addition, preclinical studies show that aged garlic extract, by virtue of its high antioxidant content, can ameliorate side effects of chemotherapeutic agents, preventing doxorubicin-induced cardiotoxicity and methotrexate and 5-fluorouracil-induced liver toxicity,⁵⁶ suggesting a potential role in cancer treatment.

Curcumin

Curcumin, the yellow pigment in tumeric and a potent anti-inflammatory and cancer-preventive antioxidant in experimental systems, is widely used in Asian countries; epidemiological studies have attributed the low rate of colon cancer in these countries to the high consumption of curcumin. Recent studies show that curcumin can induce apoptosis in colon cancer cells and multiple myeloma cells⁵⁷ as well as ovarian cancer cells.⁵⁸ Curcumin has been found to suppress the activity of the antiapoptotic protein Bcl-2 in myeloma cells and in colon cancer cells.⁵⁷

Silibinin

Silibinin is a product of milk thistle (a plant in the same family as artichoke) and similar to sylimarin, known for powerful antioxidant activity. Silibinin induces apoptosis in prostate cancer cells, suggesting a potential role in the control of the disease.⁵⁹

Resveratrol

An important component of grapes, wine, and other grape products, as well as peanuts, resveratrol has gained much interest in experimental models as a health-promoting substance because of its antioxidant properties and its cancer-preventive activity. More recent work reveals that resveratrol has potential in cancer therapy by inducing apoptosis. Studies on cancer cells from human breast, pancreas, and colon show that resveratrol triggers apoptosis in these cells⁶⁰ by controlling the proapoptotic protein Bax and activating apoptotic caspases.

Green Tea

Green tea is rich in antioxidants and consumed at high levels in Asian countries. Its protection against free radical damage is considered one of the factors responsible for the lower rate of free radical-associated pathological conditions seen in populations in Asia. Green tea extract, and more effectively, its major compound (-)epigallocatechin-3 gallate (EGCG), prevents apoptosis in normal cells exposed to free radical-producing agents⁶¹ while inducing apoptosis in tumor cells by the activating caspase 3.⁶²

Other Phytochemicals

A wide range of other phytochemicals offer protection against carcinogenic damage, preventing toxicity in normal cells during cancer therapy^{9,63} and helping to induce death signals in cancer cells, which will help reduce the tumor. Additional clinical research is needed to test the role of phytochemicals in adjuvant cancer therapy.

Conclusion

Epidemiological studies link the intake of antioxidant-rich foods with a reduced risk of certain cancers; many people in the United States consume antioxidant supplements, sometimes in large doses, in an effort to stave off disease, including cancer and other age-related conditions. Yet many questions remain unanswered and require additional research. Questions include, for example, which antioxidants are most protective? Are isolated antioxidants, taken as supplements, as effective as those acquired from food? What are optimal doses under different circumstances of risk, gender, and age and for populations with different genetic profiles? What is the role of antioxidants once cancer has been diagnosed, and what are the risks/benefits in taking antioxidants during cancer treatment by radiation or anticancer drugs?

Antioxidants protect against oncogenic transformation by radiation and free radical-producing

anticancer drugs⁶⁴ in experimental systems; we do not have, however, comparable controlled human studies that show the same association. Antioxidants do reduce the painful side effects of radiation and chemotherapy, thus supporting the beneficial effects of antioxidants in protecting normal cells during treatment and acting as adjuvants in the treatment of certain cancers. It is doubtful whether taking antioxidant supplements at government-recommended doses (recommended dietary allowance) would hinder therapy, given the high doses of radiation and anticancer drugs that are used in treatment, which deplete endogenous antioxidants; there is good evidence that antioxidants would protect normal cells during treatment and prevent treatment-associated adverse side effects.

Experimental studies show that antioxidants, including phytochemicals, selectively kill cancer cells by apoptosis while preventing apoptosis in normal cells, in vitro and in vivo, and inhibiting tumor angiogenesis and metastatic growth. Additional studies are needed to shed light on the use of antioxidants in the prevention and therapy of human cancer.

Most radiation oncologists counsel their patients to refrain from taking antioxidant supplements during cancer therapy; others, however, consider the available data and suggest that a cautious and judicious use of antioxidants that helps the patient maintain a good quality of life is useful in cancer treatment.

References

1. American Cancer Society. ACS statistics 2004. Available at: <http://www.cancer.org>. Accessed August 25, 2004
2. Gutteridge JMC. Free radicals in disease processes: a compilation of cause and consequence. *Free Radic Res Commun*. 1993;19:141-158.
3. Borek C. Free radical processes in multistage carcinogenesis. *Free Radic Res Comm*. 1991;12:745-750.
4. Borek C. Antioxidants and cancer. *Sci Med (Phila)*. 1997;4:51-62.
5. Borek C, Ong A, Mason H, Donahue L, Biaglow, JE. Selenium and vitamin E inhibit radiogenic and chemically induced transformation in vitro via different mechanisms. *Proc Natl Acad Sci U S A*. 1986;83:1490-1494.
6. Khanzode SS, Muddeshwar MG, Khanzode SD, Dakhale GN. Antioxidant enzymes and lipid peroxidation in different stages of breast cancer. *Free Radic Res*. 2004;38:81-85.
7. Steinmetz KA, Potter JD. Vegetables, fruit and cancer prevention: a review. *J Am Diet Assoc*. 1996;96:1027-1039.
8. Coia LR, Moyland, DJ. *Introduction to Clinical Radiation Oncology*. Madison, Wis: Medical Physics Publishing; 1998.
9. Borek C. Antioxidants and radiotherapy. *J Nutr*: In press.
10. Zimmermann KC, Bonzon C, Green DR. The machinery of programmed cell death. *Pharmacol Ther*. 2001;92:57-70.
11. Sigounas G, Anagnostu A, Steiner M. D α -tocopherol induces apoptosis in erythroleukemia, prostate and breast cancer cells. *Nutr Cancer*. 1997;28:30-35.
12. Borek C, Pardo F. Vitamin E and apoptosis: a dual role. In: Pasquier C, ed. *Biennial Meeting of the Society for Free Radicals Research International*. Paris, France, July 16-20, 2002. Bologna, Italy; Monduzzi Editore; 1994:327-331.

13. Taper HS, Jamison JM, Gilloteaux J, Summers JL, Calderon PB. Inhibition of the development of metastases by dietary vitamin C:K3 combination. *Life Sci.* 2004;75:955-967.
14. Ashino H, Shimamura M, Nakashima H, et al. Novel function of ascorbic acid as an angiostatic factor. *Angiogenesis.* 2003;6:259-269.
15. Kennedy, M Brunuinga K, Mutlu EA, Losurdo J, Choudhary, S, Keshavarian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol.* 2001;96:1080-1084.
16. Greenwald P, Clifford CK, Milner JA. Diet and cancer prevention. *Eur J Cancer.* 2001;37:948-965.
17. Borek C. Antioxidant health effects of aged garlic extract. *J Nutr.* 2001;131:1010S-1015S.
18. Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC. Green tea and risk of breast cancer in Asian Americans. *Int J Cancer.* 2003;106:574-579.
19. Zhang M, Binns CW, Lee AH. Tea consumption and ovarian cancer risk: a case control study in China. *Cancer Epidemiol Biomarkers Prev.* 2002;11:713-718.
20. Virtamo J, Pientinen P, Huttunen JK, et al. Incidence of cancer mortality, following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. *JAMA.* 2003;290:476-485.
21. Helzlsouer KJ, Huang HY, Alberg AJ, et al. Association between alpha tocopherol, gamma tocopherol, selenium and subsequent prostate cancer. *J Natl Cancer Inst.* 2000;92:2018-2023.
22. Li H, Stampfer MJ, Giovannucci EL, et al. A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst.* 2004;96:696-703.
23. Zhuo H, Smith AH, Steinmaus C. Selenium and lung cancer: a quantitative analysis of heterogeneity in the current epidemiological literature. *Cancer Epidemiol Biomarkers Prev.* 2004;13:771-778.
24. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA.* 1996;276:1957-1963.
25. Klein EA, Thompson IM, Lippman SM, et al. SELECT: the selenium and vitamin E cancer prevention trial. *Urol Oncol.* 2003;21:59-65.
26. Sato R, Helzlsouer KJ, Huang HY, et al. Prospective study of carotenoids, tocopherol, and retinoid concentrations and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2002;11:451-457.
27. National Institutes of Health. Information on clinical trials. Available at: <http://clinicaltrials.gov>. Accessed August 25, 2004.
28. Sangeetha P, Das UN, Koratkar R, Suryaprabha P. Increase in free radical generation and lipid peroxidation following chemotherapy in patients with cancer. *Free Radic Biol Med.* 1990;8:15-19.
29. Weijl NI, Hopman GD, Wipkink-Bakker A, Lentjes EGWM, Berget HM. Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. *Ann Oncol.* 1998;9:1331-1337.
30. Sozen S, Coskun U, Sancak B, et al. Serum levels of interleukin-18 and nitrite + nitrate in renal cell carcinoma patients with different tumor stage and grade. *Neoplasma.* 2004;51:25-29.
31. Lenton KJ, Greenstock CL. Ability of human plasma to protect against ionizing radiation is inversely correlated with age. *Mech Ageing Dev.* 1999;107:15-20.
32. Young AJ, Lowe GM. Antioxidant and prooxidant properties of carotenoids. *Arch Biochem Biophys.* 2001;385:20-27.
33. Rodemann HP, Hehr T, Bamberg M. Relevance of the radio-protective effect of sodium selenite. *Med Klin (Munich).* 1999;94(suppl 3):39-41.
34. Ip C, Dong Y, Ganther HE. New concepts in selenium chemoprevention. *Cancer Metastasis Rev.* 2002;21:281-289.
35. Jonsson-Videstar K, Bjorkhem-Bergman L, Hossain A, et al. Selenite-induced apoptosis in doxorubicin-resistant cells and effects on the thioredoxin system. *Biochem Pharmacol.* 2004;67:513-522.
36. Prasad KN, Kumar B, Yan XD, Hanson AJ, Cole WC. Alpha tocopheryl succinate the most effective form of vitamin E for adjuvant cancer treatment: a review. *J Am Coll Nutr.* 2003;22:108-117.
37. Haendeler J, Zeiher AM, Dimmler S. Vitamin C and vitamin E prevent lipopolysaccharide-induced apoptosis in human endothelial cells by modulating Bcl-2 and Bax. *Eur J Pharmacol.* 1996;17:407-411.
38. Kagerud A, Peterson HI. Tocopherol in irradiation of experimental neoplasms: influence of dose and administration. *Acta Radiol Oncol.* 1981;20:97-100.
39. Barnett KT, Fokum FD, Malafa MP. Vitamin E succinate inhibits colon liver metastases. *J Surg Res.* 2002;106:292-298.
40. Malafa MP, Fokum FD, Smith L, Louis A. Inhibition of angiogenesis and promotion of melanoma dormancy by vitamin E succinate. *Ann Surg Oncol.* 2002;9:1023-1032.
41. Fleischauer AT, Simonsen N, Arab L. Antioxidant supplements and risk of breast cancer recurrence and breast cancer related mortality among postmenopausal women. *Nutr Cancer.* 2003;46:15-22.
42. Shin DM, Khuri FR, Murphy B, Gardens AS, Clayman G. Combined interferon-alpha, 13 cis-retinoic acid, and alpha tocopherol in locally advanced head and neck squamous cell carcinoma: novel biodjuvant phase II trial. *J Clin Oncol.* 2001;19:3010-3017.
43. Behl C, Moosmann R. Oxidative nerve cell death in Alzheimer's disease and stroke: antioxidants as neuroprotective compounds. *Biol Chem.* 2002;383:521-536.
44. Delanian, Bella Mekias S, Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J Clin Oncol.* 1999;17:3283-3290.
45. Peter RU, Gottlober P. Management of cutaneous radiation injuries: diagnostic and therapeutic principles of the cutaneous radiation syndrome. *Military Med.* 2002;167(suppl 1):110-112.
46. Wejl NI, Elsendoorn TJ, Lentjes EGWM, et al. Supplementation with antioxidant micronutrients and chemotherapy induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomized double blind placebo-controlled study. *Eur J Cancer.* 2004;40:1713-1723.
47. Wejl NI, Cleton FJ, Osanto S. Free radical and antioxidants in chemotherapy induced toxicity. *Cancer Treat Rev.* 1997;23:574-579.
48. Lopez I, Goudou C, Ribrag V, Sauvage C, Hazebroucq G. Treatment of mucositis with vitamin E during administration of neutropenic antineoplastic agents [in French]. *Ann Med Interne (Paris).* 1994;92:405-408.
49. Wagdi P, Fiuri M, Aeschbacher B, Fikrie A, Meier B. Cardio-protection in patients undergoing chemo- and/or radiotherapy for neoplastic disease: a pilot study. *Jpn Heart J.* 1996;37:353-359.
50. Borek C. Anti-aging effects of CoQ10. *AgroFood Industry Hi-Tech.* 2004;15:24-27.
51. Iarussi D, Auricchio U, Agretto A, Murano A, Giuliano M. Protective effects of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Mol Aspects Med.* 1994;15(suppl):s207-s212.
52. Amagase H, Petesch BL, Matsura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive compounds. *J Nutr.* 2001;131(suppl 3):955S-962S.
53. Kyo E, Uda N, Kasuga S, Itakura Y. Immunomodulatory effects of aged garlic extract. *J Nutr.* 2001;133:1075S-1079S.

54. Pinto JT, Rivlin RS. Antiproliferative effects of allium derivatives from garlic. *J Nutr*. 2001;131(suppl 3):1058S-1060S.
55. Xiao D, Pinto JT, Soh JW, et al. Induction of apoptosis by the garlic derived compound S-allylmercaptocysteine (SAMC) is associated with microtubule depolymerization and c-Jun NH2-terminal kinase 1 activation. *Cancer Res*. 2000;63:6825-6837.
56. Kojima R, Epstein CJ, Mizui T, Carlson E, Chan PH. Protective effects of aged garlic extracts on doxorubicin-induced cardiotoxicity in the mouse. *Nutr Cancer*. 1994;22:163-173.
57. Chauhan DP. Chemotherapeutic potential of curcumin for colorectal cancer. *Curr Pharm Des*. 2002;8:1695-1706.
58. Zheng L, Tong Q, Wu C. Growth inhibitory effects of curcumin on ovary cells and its mechanism. *J Huazhong Univ Sci Technolog Med Sci*. 2004;24:55-58.
59. Tyagi A, Bahtia N, Condon MS, Bosland MC, Agarwal C, Agarwal R. Antiproliferative and apoptotic effects of silibinin in rat prostate cancer cells. *Prostate*. 2002;53:211-217.
60. Ding XZ, Adrian TE. Resveratrol inhibits proliferation and induces apoptosis in human pancreatic cancer cells. *Pancreas*. 2002;25:E71-E76.
61. Nie G, Cao Y, Zhan B. Protective effects of green tea polyphenols and their major component (-)epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells. *Redox Rep*. 2002;7:171-177.
62. Hsu S, Lewis J, Singh B, et al. Green tea polyphenol targets the mitochondria in tumor cells inducing caspase 3 dependent apoptosis. *Anticancer Res*. 2003;23:1533-1539.
63. Weiss JF, Landauer MR. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. *Toxicology*. 2003;189:1-20.
64. Borek C, Troll W. Modifiers of free radicals inhibit in vitro the oncogenic actions of x-rays, bleomycin, and the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate. *Proc Natl Acad Sci U S A*. 1983;80:1304-1307.