Special Series

Dietary Antioxidants, Cancer, and Atherosclerotic Heart Disease

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Highlights

- Considerable evidence indicates that oxidative processes contribute to the development of degenerative diseases, including cancer and atherosclerotic heart disease.
- Dietary antioxidants such as vitamins C and E and β-carotene are important components of the body's defense against pathophysiologic oxidation events and, on this basis, have been proposed to protect against disease.
- Claims for the health benefits of diets rich in fruits, whole grains, and vegetables, which are naturally antioxidant-rich, cholesterol-free, and fat-poor, appear well-founded given the consistency of epidemiologic observations to this effect.
- The routine practice of antioxidant supplementation cannot be advocated on a population-wide basis because few direct prospective data of a beneficial effect have been obtained.

Antioxidants, including vitamin C, vitamin E, and β-carotene, have long been proposed to be disease-preventing agents by health activists and, more recently, have been promoted as such by members of the medical and scientific establishment. The growing interest in antioxidants stems from increasing recognition of the potentially pervasive role of oxidation in the development of diseases such as cancer and heart disease and the possibility that antioxidants may counteract disease-promoting oxidation events.[1] We provide an overview of the theoretical basis for a preventive role of antioxidants, describe studies in which this role has been examined, and consider whether currently available evidence supports claims for the health benefits of antioxidant supplementation.

Oxidants and Disease

Partially reduced forms of oxygen including superoxide (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical (•OH), and organic counterparts such as lipid hydroperoxides are produced during aerobic metabolism. These agents are capable of reacting with and causing oxidative injury to macromolecules including nucleic acids, proteins, lipids, and carbohydrates and thus are referred to collectively as oxidants.[1-8] Some oxidants are free radicals, which are particularly reactive due to the presence of an unpaired electron, and are capable of initiating radical chain reactions that can cause rapid spread and amplification of oxidative injury in biologic systems. Because of the possible toxicity of oxidants, numerous counteractive antioxidants have evolved to intercept and effectively deactivate these agents. The antioxidant network is not fool-proof, however, and under certain conditions such as inflammation and xenobiotic metabolism, oxidants may be produced in amounts that exceed antioxidant capacity.

Oxidative injury is suggested to be a common disease mechanism, with disease end points differing according to the identity and tissue location of the injured substrate(s). Consistent with a pervasive role in disease, oxidants have been implicated in such diverse conditions as cancer, atherosclerotic heart disease, stroke, arthritis, cataract formation, Parkinson's disease, and drug toxicity.[1-8] Because of the prevalence and the human and financial consequences of cancer and heart disease in Western societies, however, we will focus on these conditions.

Cancer

Cancer evolves from a multistage process culminating in the development and spread of cell populations that are unresponsive to the normal controls over cell proliferation.[8] DNA damage is an early event in carcinogenesis and occurs in essentially two steps: an initial DNA insult that is reparable, followed by permanent fixation of the injury, if DNA replicates before the injury is repaired.[9-11] Numerous types of modifications, including oxidation, are known to damage DNA.[12-14] Oxidative DNA damage may lead to the formation of DNA-protein cross-links, alterations in the carbohydrate backbone, or direct modifications of the purine and pyrimidine bases.[15] Oxidative

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ABBREVIATIONS USED IN TEXT

LDL = low-density lipoprotein
RDA = recommended dietary allowance

injury to DNA bases, which can result in mutations, appears to be a common occurrence in vivo. Based on determinations of urinary levels of 8-hydroxydeoxyguanosine, researchers have estimated that steady-state levels of oxidatively modified bases are as high as 10^5 in humans, with approximately 10^4 formed every day.[13,14] This occurrence rate carries with it a high likelihood that a substantial number will escape repair mechanisms and lead to a permanent change in the DNA base sequence upon replication. Oxidants also have been shown to stimulate cell proliferation[14,16,17] and thereby may promote injury fixation. Malignant tumors may develop if resulting changes in the DNA lead to the activation or altered expression of oncogenes or the inactivation of tumor suppressor genes, or both.[18-21]

The promotion of preneoplastic changes in "initiated" cells, that is, cells with alterations in the DNA that can lead to cancer, and the progression of premalignant lesions also may involve oxidants.[22-24] Because these phases occur over a much longer time frame than initiation, however, the specific events and role of oxidants are less well-defined. It is suggested that the oxidation-antioxidation potential may be particularly important in determining the "permissiveness" of the system for tumor development, in that an oxidizing environment may be more conducive for development.[22,24]

Atherosclerosis

Atherosclerosis results from the accumulation of cholesterol and the proliferation of cellular elements in the arterial wall. Considerable evidence now indicates that oxidation increases the ability of low-density lipoproteins (LDLs) to promote cellular alterations that lead to atherosclerosis.[6,7,25-39] Unlike native (nonoxidized) LDL, oxidized LDL is taken up at rapid rates by scavenger receptors on macrophages, leading to the formation of lipid-laden foam cells that form the basis of early fatty-streak lesions.[26,27] In addition, oxidized LDL may recruit circulating monocytes to the region of the developing plaque[28-30] and alter the behavior and viability of surrounding cells.[31-35]

Growing chemical and immunologic evidence supports the existence of oxidatively modified LDL in vivo.[36-39] Oxidized LDLs have been identified in atheromatous lesions,[36,37] and autoantibodies against oxidized LDL (malondialdehyde-modified LDL) have been detected in serum from both rabbits and humans.[38,39] Furthermore, in humans, the oxidized LDL autoantibody titer has been shown to be a predictor of subsequent carotid atherosclerosis progression.[39] A direct causal link between oxidized LDL and the development of atherosclerosis, however, has not been established.

Low-density lipoproteins can be oxidized in vitro by incubation with cells derived from the arterial wall,[6,7,25,40,41] and this is a plausible means of oxidation in vivo. Susceptibility to oxidation differs among LDL preparations and is suggested to contribute to differences in LDL atherogenicity.[42-47] Lesion development may thus be a function of both levels of LDL, which is well-documented experimentally, and the tendency of these particles to undergo oxidative modification.[6] In support of a role for the latter, LDL oxidative susceptibility was recently shown to be greater in patients with angiographically proven coronary artery disease.[47] The degree to which LDL oxidative susceptibility in vitro reflects the oxidative behavior of LDL in vivo has yet to be determined. Nonetheless, much research effort is now being directed toward identifying factors, including antioxidants, that influence LDL oxidative susceptibility.

Antioxidants as Disease-Preventing Agents

Aerobic organisms are protected from the toxic effects of reactive oxygen species by a multilevel antioxidant defense network that includes agents capable of preventing or reducing oxidant generation, agents that intercept oxidants before their interaction with other biologic components, and agents that repair oxidant-induced injury.[45] Dietary micronutrients are indispensable components of the antioxidant network and include vitamin C (ascorbic acid), vitamin E (comprising tocopherols and tocotrienols, of which α-tocopherol is the predominant and most active form), and β-carotene. Vitamin C serves as a potent radical-scavenging agent in the aqueous phase, whereas vitamin E and β-carotene intercept radicals within lipid environments. The critical importance of vitamin E derives from its role as the last line of defense against oxidative injury to lipids by preventing radical chain propagation.[46]

Although not discussed in detail in this review, minerals such as selenium, copper, zinc, and manganese also function in the antioxidant network, primarily by acting as cofactors for enzymes with antioxidant activity.[48] Selenium may be particularly important in protecting the lipid environment against oxidative injury through its role as a cofactor for glutathione peroxidase, which catalyzes the reduction of lipid hydroperoxides.[48]

As evidence has accumulated in support of a role for oxidative processes in disease, attention has focused on the possible preventive properties of antioxidants. Dietary antioxidants have received particular attention in this regard because exposure to these agents varies widely among populations and can be readily manipulated by dietary changes, supplementation, or both. A preventive role for these agents is supported by several lines of evidence. Epidemiologic studies have shown a relationship between antioxidant nutriture, as indicated by food consumption patterns or direct measures of tissue concentrations of these agents, and the risk of cancer and atherosclerotic heart disease in humans.[49-59] In some cases, induced deficiencies of antioxidant micronutrients have been shown to promote,[49] while antioxidant supplementation has been shown to inhibit, carcinogenic and atherogenic processes in animals.[49,60-67] In addition, detailed

biochemical-mechanistic studies in model systems have shown that antioxidants can directly modulate relevant pathophysiologic events in vitro.[48,49,60,61,68-71] Notably missing, however, is direct evidence from randomized, placebo-controlled trials of the protective effects of antioxidants in human populations that are initially free of disease. This is considered to be the definitive test for putative antidisease agents. Several large-scale, long-term antioxidant intervention trials are currently either underway or in the planning stages[72-77] and within the coming decade are expected to expand our knowledge of the preventive properties of antioxidants.

Cancer

Dietary habits have been implicated in as much as 60% of all environmentally linked cancers, although most estimates are closer to 30%.[78] Epidemiologic studies have consistently shown that a reduced intake of fruits and vegetables, which are rich in antioxidants (Table 1),[79-81] is a major risk factor for the development of cancers of the lungs, pancreas, liver, bowel, ovaries, endometrium, cervix, and prostate.[52,53,56] Although this may partially reflect the higher fat consumption that often accompanies reduced fruit and vegetable intake,[82] evidence suggests a direct protective effect of these food groups, and this has been attributed to the presence of specific micronutrients, including vitamin C and β-carotene. Consistent with this hypothesis, indices of vitamin C and β-carotene nutriture have been shown to be inversely associated with the risk of non–hormone-dependent cancers.[51,53,57] Moreover, in cellular and organ systems and in animals, high levels of these agents have been shown to directly inhibit exposure-induced mutagenicity, malignant transformation, and tumor formation.[50,60]

Antioxidant mechanisms have been suggested to underlie the putative anticancer properties of vitamin C and β-carotene. These agents have other properties that may be important in this regard, however. Vitamin C directly suppresses carcinogen formation, enhances immunocompetence, participates in collagen synthesis, and inhibits hyaluronidase activity (which contributes to the breakdown of a mucopolysaccharide that acts as an intracellular cement).[50,51,83] The relative importance of these properties is unknown, but may vary depending on the tissue involved. β-Carotene is a precursor of vitamin A, which has well-known antitumor effects in animals, likely arising from its role in promoting cell differentiation, and could thus contribute to any observed preventive effects of β-carotene.[8,60,82] Carotenoid pigments without vitamin A activity, such as canthaxanthin and phytoene, have been shown to reduce tumor formation in animals, however, and their relative protective effects appear to correspond with their abilities to quench reactive oxygen species.[82]

In contrast to the findings for vitamin C and β-carotene, results from epidemiologic studies examining the relationship between dietary vitamin E and cancer risk have been equivocal.[84-86] Several prospective studies have noted slightly lower plasma levels of this micronutrient in persons in whom cancers subsequently developed relative to matched controls. In a recent large cohort study in Finland, for example, persons with low serum α-tocopherol concentrations had about a 1.5-fold greater risk of cancer developing, particularly gastrointestinal and uterine cancer, than those with higher levels.[54] These results are consistent with studies indicating that vitamin E inhibits exposure-induced cancers in animals.[62]

In a recently published study, disease-protective effects of antioxidant supplements were observed in a large population (>30,000 adults) in China.[87] The authors noted a substantial lowering of all-cause mortality in persons given a supplement daily for five years of the antioxidant nutrients β-carotene, vitamin E, and selenium at doses ranging from one to two times the United States recommended dietary allowance (RDA). Reduced mortality was attributed to lower rates of cancer (13%), especially of stomach cancer (21%). In contrast, no effects were observed for supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum. Although this study supports the possible benefit of specific antioxidant micronutrients as chemopreventive agents, because this study population has one of the world's highest rates of esophageal-gastric cardia cancer, together with persistently low intakes of fruits and vegetables, the applicability of these results to other populations is unclear. The effects of dietary supplementation that reduce nutrient deficiencies, which appears to have been the case in this study, may be fundamentally different from the effects of larger doses in better nourished populations.

Contrary to a chemopreventive role, recent results from the α-Tocopherol, β-Carotene Cancer Prevention Study have raised the possibility that antioxidant supplementation may actually have adverse effects in certain populations.[88] In this randomized, double-blind, placebo-controlled primary prevention trial, the effects on cancer incidence of long-term—5 to 8 years—daily supplementation with α-tocopherol (50 mg per day), β-carotene (20 mg per day), or a combination of the two were monitored in more than 29,000 Finnish male smokers.[88] No reduction in the incidence of lung cancer was observed among those receiving α-tocopherol, although there were fewer new cases of prostate cancer. Surprisingly, a higher incidence of lung cancer was noted in persons receiving β-carotene supplementation, and as a result of deaths from lung cancer and ischemic heart disease, total mortality was 8% higher. The effects of antioxidant supplementation in smokers may be different from those in nonsmoking populations. Morever, antioxidants may be most effective as preventive agents early in the disease process, and thus may be of little value after long-term smoke exposure. The epidemiologic link between lung cancer and β-carotene is among the strongest, however, and given that smokers make up the bulk of victims of lung cancer, the results are of considerable importance in terms of the limitations of antioxidant supplements and the possibility of adverse effects.

Atherosclerosis

Cross-cultural comparisons have indicated a strong inverse relationship between levels of plasma vitamin E and

heart disease mortality in humans. A significant inverse association has been found between plasma vitamin E levels in population cohorts and heart disease mortality rates among 16 European communities.[49,55] Lipid-standardized levels of plasma vitamin E and plasma vitamin E plus cholesterol were found to predict 62% and 79%, respectively, of the variance in heart disease mortality.[55] In contrast, only a modest nonsignificant association was observed for vitamins A and C. Although the results for vitamin E are intriguing, other interpopulation differences not measured may have a greater influence on disease risk.

Investigations within populations, including a number of case-control studies published over the past decade, generally have not supported an association between plasma vitamin E levels and heart disease risk. In a five-year prospective study associated with the Eastern Finland Heart Study, no difference was found in serum vitamin E concentrations between 92 victims of fatal myocardial infarction and controls matched for sex, age, smoking status, plasma cholesterol level, mean arterial pressure, and history of heart disease.[89] In the prospective Basal Study, mean cholesterol-standardized plasma vitamin E levels were not substantially lower for 67 persons who died of ischemic heart disease during the subsequent seven years than in survivors.[85] Notably, however, these studies involved measurements of antioxidants in single rather than multiple plasma specimens that had been stored long term, under conditions in which they may be unstable.

In a recently published analysis of data from more than 11,000 adults in the United States examined in the first National Health and Nutrition Examination Survey (NHANES I), a significantly reduced risk of subsequent death from all causes, particularly coronary heart disease, was observed in persons reporting a high intake of vitamin C (more than 300 to 400 mg per day).[57] A reduced risk was especially apparent in men; those in the high-intake group had an increased life expectancy of more than six years relative to those consuming less than 50 mg per day. In contrast, no evidence of a protective effect of high vitamin C intake was found in a large-scale prospective study involving more than 40,000 men and 80,000 women, but a reduced risk of coronary artery deaths was found in men and women with higher intakes of vitamin E (100 IU per day or more for two years or more).[58,59]

Although epidemiologic associations do not allow the assignment of cause and effect, some evidence for direct protective effects of antioxidants comes from animal experimentation. Induced deficiencies of vitamin C and vitamin E have been shown to result in atherosclerotic-like lesions.[49] Conversely, supplementation with these and other antioxidants has been found in some but not all cases to reduce lesion growth in hypercholesterolemic animals.[49,63-67] The extent of protection ranges from slight to pronounced, with differences likely arising from variations in animal models, antioxidant identity and dose, study duration, and atherosclerosis assessment methods. In several studies, the antiatherogenic effects of antioxidants have been shown to be greater when these agents are supplied in combination, such as vitamin E and selenium.[65]

Although vitamins C and E also produce minor beneficial alterations in plasma lipid levels, their primary protective effects are suggested to arise from their antioxidant properties. In support of this, two studies have shown protection by vitamin E even in the absence of reductions in plasma cholesterol levels.[63,64] Other effects of these nutrients also may be relevant, however. For example, differences were recently observed in the content of cell surface constituents in the endothelium of cholesterol-fed guinea pigs, depending on whether or not they also received vitamin E.[67]

Lipophilic antioxidants potentially could be particularly effective as antiatherogenic agents by virtue of their localization within the LDL particle, where they directly inhibit LDL oxidation. The oxidative resistance of LDL has been shown to be greater when vitamin E levels are increased either in vitro or through dietary vitamin E supplementation.[46,47,71,87] Whereas the addition of β-carotene in vitro has been shown to reduce LDL oxidative susceptibility,[70] β-carotene enrichment through dietary supplementation does not appear to have such effects.[90] In contrast to these antioxidants, vitamin C does not circulate within LDL, but may protect this lipoprotein by intercepting oxidants in the aqueous compartment and possibly by regenerating LDL-associated α-tocopherol (vitamin E) from the α-tocopheroxyl radical at the lipid-water interface. Although evidence of a tocopherol-sparing effect of vitamin C has been obtained for LDL in vitro,[68,69] this property has not been demonstrated in vivo.

In addition to the direct inhibition of LDL oxidation, antioxidants may reduce cellular oxidation events involved in atherosclerosis. As an example of this, cells loaded with the lipophilic antioxidant drug probucol were shown to be much less effective in bringing about the oxidative modification of LDL.[91] An elevated cellular antioxidant capacity also may reduce their sensitivity to the toxic effects of oxidized LDL.

Arguments for and Against Antioxidant Supplementation as a Disease-Preventing Measure

Given the increasing evidence of a role for oxidative processes in the development of chronic diseases and the possibility that specific antioxidants may protect against such processes, it has been suggested that increasing the intake of antioxidants through supplementation may prevent disease. Recommendations regarding micronutrient intake traditionally have been based on the concept of minimum requirements for avoiding deficiency symptoms.[79] Such constructs may be inappropriate when considering possibly protective dietary factors because levels that are adequate for preventing deficiency are not likely to provide for optimal tissue function, particularly in the presence of environmental stresses unique to modern society. As described earlier in this review, results from the

trial in Linxian, China, showed that low-dose supplementation with certain antioxidants reduced cancer mortality in an initially poorly nourished population,[87] and results of other studies raise the possibility that higher intakes of antioxidants may reduce the risk for chronic disease in the better-nourished population in the United States.[57-59] In these studies, apparently "protective" levels of vitamin C or vitamin E—5 to 10 times the RDA—exceeded those attained through normal dietary intake alone.[58-60]

Opponents of antioxidant supplementation point out that there is little direct evidence of protective effects in humans. Furthermore, although the safety of vitamin supplements that contain 100% of the RDAs is well-accepted,[92] the side effects of long-term supplementation with higher levels have not been examined prospectively.[74,75] Few serious symptoms of toxicity for these nutrients have been described (Table 1), but this may simply reflect the lack of studies addressing this issue. In a recent report, low-dose α-tocopherol supplementation was found to preserve endothelial vasodilator function in cholesterol-fed rabbits, whereas high-dose supplementation was associated with endothelial dysfunction and enhanced intimal proliferation.[93] It is possible that this dichotomy in response to low- versus high-dose antioxidants also may occur in humans. Results of the study in Finnish male smokers raise the possibility that long-term β-carotene supplementation at levels 10 to 20 times higher than in the US diet may actually be deleterious.

Apart from these arguments, most of the epidemiologic studies indicating health benefits from increased antioxidant intake are based on the assessment of dietary patterns rather than direct measures of intake of these specific micronutrients. Nutrient-based recommendations derived from food intake patterns fail to consider the importance of nutrient interactions or the possibility that other as-yet-unrecognized factors may underlie associations between dietary antioxidant intake and disease risk. Fruits and vegetables also contain appreciable levels of minerals, flavonoids, and indoles as well as carotenoids other than β-carotene, and these or other agents may have protective properties.[52]

Indeed, before definitive recommendations can be made regarding the prophylactic use of antioxidants, the following questions need to be addressed in humans:

- Do antioxidant vitamins actually prevent or reduce the development of chronic diseases? If so, which antioxidants are most effective in preventing disease and at what doses?
- How do the possible benefits and optimal doses vary in relation to the nature and stage of the disease?
- Do antioxidants have a role in secondary prevention?
- Are there interactions among antioxidants or between antioxidants and other dietary factors, such as fat composition, that influence their effectiveness?
- How do genetic and environmental factors—cigarette smoke exposure, for example—influence antioxidant nutriture or effectiveness in preventing disease?
- Are toxic effects of long-term antioxidant supplementation observed at doses required for disease prevention?

A number of prospective trials addressing some of these questions in US populations are currently underway.[74-77] Among these are the following:

- The Physicians' Health Trial, a study involving 22,000 men taking either β-carotene or a placebo, which is scheduled for completion in 1996;
- The Women's Health Study, an investigation of the preventive effects of β-carotene, vitamin E, and aspirin in women older than 50 years, which was begun in 1992; and
- The Carotene and Retinoid Efficacy Trial (CARET), a study examining the ability of β-carotene plus retinyl palmitate to reduce lung cancer incidence in 18,000 men and women who are either smokers or who

TABLE 1.—*Natural Sources, Physiologically Relevant Doses, and Side Effects of Antioxidants in Humans*

Antioxidant	*Dietary Sources*	*Recommended Dietary Allowance**	*Toxicity Level†*	*Reported Side Effects at High Doses†*	*Contraindications†*
Vitamin C	Fruits (particularly citrus), green leafy vegetables, tomatoes, potatoes	Nonsmokers: 60 mg/day Smokers: 100 mg/day	Adverse effects observed at doses of ≥1 gram/day	Urinary oxalate excretion, kidney stone formation, increased iron absorption, gastrointestinal disorders	Renal insufficiency, iron overload
Vitamin E	Vegetable oils, whole grains, nuts and seeds, green leafy vegetables	Men: 15 IU/day Women: 12 IU/day	No consistent adverse effects with doses up to 3,000 IU/day for months	Fatigue and weakness, gastrointestinal disorders, breast soreness (women), bleeding	Subjects receiving vitamin K antagonists as anticoagulants
β-Carotene	Green leafy vegetables, yellow-orange fruits, and vegetables	None established‡	Appears to be nontoxic even when taken in large doses over years	Carotenodermia (presumed innocuous)	

*Values are for adults (≥19 years of age); taken from the National Research Council.[79]
†From the National Research Council,[79] Sestili,[80] and Bendich and Machlin.[81]
‡The typical United States diet contains 1 to 2 mg/day, or 1,700 to 3,500 IU/day.

have a history of asbestos exposure.

Based on current knowledge and regard for scientific data as a basis for clinical decision making, advocating proper food selection with a high intake of fruits and vegetables should be the primary message of the health care community in response to the growing interest in antioxidants. This approach avoids the possibility of toxic side effects from supplements and emphasizes the role of the total diet in determining disease risk.[75] As few as 10% of Americans are estimated to consume five servings of fruits and vegetables per day.[56,94] Thus, there is much room for beneficial changes in the eating habits of the US population.

Populations With Increased Antioxidant Needs

Special consideration should be given to persons likely to be at increased risk of inadequate antioxidant intakes due to genetic or environmental factors that may increase antioxidant requirements. Although still relatively unexplored, several specific factors affecting individual antioxidant requirements have been identified. The best-known example is cigarette smoke, which contains numerous oxidants and appears to increase endogenous oxidant production.[95-99] Severe depletions of circulating antioxidants, presumably indicative of reduced body stores, are a measurable effect of the oxidant burden imposed by cigarette smoke. Reductions in plasma vitamin C levels as great as 75% have been reported in smokers compared with nonsmokers, depending on age, sex, and smoking history.[100-105] Although reduced vitamin C consumption and bioavailability are possible contributors,[106,107] increased vitamin C turnover is largely responsible for the poor vitamin C status of smokers.[108] Reductions in lipophilic antioxidants also have been reported, with results being more consistent for β-carotene than for vitamin E.[109-112]

Recognizing the increased vitamin C requirements of smokers, the National Research Council recently increased the RDA from 60 to 100 mg per day for this subpopulation.[92] Several studies, however, have suggested that even this may not be enough.[103-105] We recently observed that plasma vitamin C concentrations were lower in heavy smokers (≥ 1 pack per day) reporting daily intakes of vitamin C greater than 250 mg as compared with nonsmokers reporting similarly high intakes. In the same study, we also observed lower plasma vitamin C levels in nonsmokers with regular exposure to environmental tobacco smoke than in nonsmokers without such exposure, even at dietary vitamin C intakes above the RDA for smokers. Thus, it appears likely that such intakes may not be adequate to maintain needed body stores in nonsmokers with exposure to tobacco smoke.[105]

The increased antioxidant requirements and risk of disease associated with exposure to tobacco smoke and other environmental agents,[77,113-115] including ultraviolet irradiation and certain food constituents such as nitrosamines, may justify recommendations for low-dose supplementation in persons with such exposure. Caution is recommended, however, because recent results have suggested that higher dose supplementation, particularly with β-carotene, may be deleterious in long-term smokers.[88] Any recommendations for antioxidant supplementation should be coupled with recommendations for reducing exposures—smoking cessation, for example.

Conclusion

The compelling evidence of a role for oxidative processes in a variety of chronic diseases is likely to lead to increased research attention to the preventive properties of antioxidants, and the results of such studies may affect approaches for preventing and treating chronic diseases. Current evidence supports recommendations for diets containing food groups that are naturally high in antioxidants. Recommendations for increasing antioxidant intake through supplementation cannot be made on the basis of current scientific evidence, however, because to date most of the data supporting a protective effect in humans are epidemiologic, and some evidence of side effects has been presented. Nonetheless, because of the widespread availability of antioxidant supplements and the mass media's promotion of their consumption, many patients will make an independent decision to supplement. Physicians may choose not to discourage such practices, particularly in high-risk patients, but may wish to provide counsel regarding the preliminary nature of scientific data supporting the benefits and evidence of possible side effects of antioxidant supplementation (see the Page for Patients at the end of this article).

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