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Review

The Antioxidant Conundrum in Cancer

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Abstract

The health-related effects of interactions between reactive oxygen species (ROS) and dietary antioxidants and the consequences of dietary antioxidant supplementation on human health are by no means clear. Although ROS, normal byproducts of aerobic metabolism, are essential for various defense mechanisms in most cells, they can also cause oxidative damage to DNA, proteins, and lipids, resulting in enhanced disease risk. Dietary antioxidants (*e.g.*, vitamin E, vitamin C, β-carotene, and selenium), as well as endogenous antioxidant mechanisms, can help maintain an appropriate balance between the desirable and undesirable cellular effects of ROS. However, any health-related effects of interactions between dietary antioxidants and ROS likely depend on the health status of an individual and may also be influenced by genetic susceptibilities. Clinical studies of antioxidant supplementation and changes in either oxidative status, disease risk, or disease outcome have been carried out in healthy individuals, populations at risk for certain diseases, and patients undergoing disease therapy. The use of antioxidants during cancer therapy is currently a topic of heated debate because of an overall lack of clear research findings. Some data suggest antioxidants can ameliorate toxic side effects of therapy without affecting treatment efficacy, whereas other data suggest antioxidants interfere with radiotherapy or chemotherapy. Overall, examination of the evidence related to potential interactions between ROS and dietary antioxidants and effects on human health indicates that consuming dietary antioxidant supplements has pros and cons for any population and raises numerous questions, issues, and challenges that make this topic a fertile field for future research. Overall, current knowledge makes it premature to generalize and make specific recommendations about antioxidant usage for those at high risk for cancer or undergoing treatment.

Introduction

Belief in the medicinal powers of dietary antioxidants as protectors of human health continues to prevail. In 2000, the National Academy of Sciences defined a dietary antioxidant in this manner: "A dietary substance in food that significantly decreases the adverse effects of ROS,[2] reactive nitrogen species, or both on normal physiological functions in humans" (1). Even though a balanced diet provides antioxidants, some people regularly take antioxidant supplements in hopes of preventing disease by slowing down the biological oxidative processes that contribute to aging and disease risk. In reality, dietary antioxidants take part in cellular reduction-oxidation (redox) reactions in which they can act as either antioxidants (electron donors) or prooxidants (electron acceptors), depending on the physiological environment and general oxidative state (2–5). ROS are normal metabolic byproducts that are generated continuously in the mitochondria in most cells (6–8). Although ROS are essential for various cell defense mechanisms, they can also cause oxidative damage to DNA, proteins, and lipids, resulting in potentially enhanced disease risk. Thus, the possibility exists that, in an environment resulting in prooxidant activity by dietary antioxidants, which can interfere with maintaining desired levels of ROS, antioxidant supplementation may actually cause harm in terms of increased risk of new disease or interference with treatment of existing disease. Numerous issues and challenges are encountered when conducting studies aimed at clarifying the effects of antioxidants on human health and when considering the use of antioxidant supplements for either disease prevention or treatment. The term "conundrum," meaning an intricate and difficult problem, seems a particularly apt way to refer to the obstacles associated with antioxidant-related research and the current inability to articulate who will or will not benefit from supplemental intakes.

Synergistic *Versus* Antagonistic Effects

One significant issue to consider is whether antioxidant supplements complement or interfere with the actions of antioxidants supplied by a normal diet. That is, how do various antioxidant supplements interact with each other and with additional dietary constituents to affect *in vivo* redox balance? Consumption of a typical American diet provides not only antioxidant vitamins and minerals such as vitamins C and E, β-carotene, and selenium, but also hundreds of phytochemicals that may accumulate within cells and that can act as antioxidants/prooxidants in the cellular environment (6, 7). For instance, vegetables and fruits contain hundreds of dietary flavonoids, structurally heterogeneous phenolic compounds characterized by the flavan nucleus, that exhibit varying degrees of antioxidant and prooxidant activity. Examples include epigallocatechin gallate (tea), quercetin (*e.g.*, onion, red wine, berries), genistein (soybean), and taxifolin [citrus fruits (9)]. Other classes of dietary phytochemicals that can take part in redox reactions in addition to the flavonoids include the broad categories of carotenoids (10) and organosulfur compounds (11). Foods vary widely, however, in their antioxidant capabilities. A recent systematic assessment of total antioxidants in vegetables, fruits, cereals, nuts, and pulses, using the ferric-reducing ability of plasma assay, found more than a 1000-fold difference among plants' edible parts; fruits of the Rosaceae family (*e.g.*, dog rose, strawberry, blackberry, sour cherry, and raspberry) contained some of the highest antioxidant levels (12). In addition, the antioxidant levels of any specific plant food will likely fall within a range that varies with growing conditions such as moisture, temperature, and soil composition and the specific plant species and variety as well as with handling and storage after harvest and food preparation methods (13). The presence of numerous naturally occurring dietary redox agents and their probable interactions with each other, with other dietary constituents, and with dietary supplements certainly contribute to the complexity of research that aims to clarify the influence of antioxidants on human health.

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[2] The abbreviations used are: ROS, reactive oxygen species; SeMet, selenomethionine; 8OHdG, 8-hydroxy-2′-deoxyguanosine; OR, odds ratio.

Upper Levels

It is important to point out that antioxidant supplements are not always safe. Toxicity can occur at very high intake levels for some commonly consumed antioxidants, but the overall incidence rate for vitamin E is only 0.8% (14). For example, in healthy adults, doses of 200–800 mg/day of vitamin E generally are tolerated with no adverse effects except for some gastrointestinal upset, 800-1200 mg/day may cause antiplatelet effects and bleeding, and doses above 1200 mg/day have resulted in infrequent complaints of headache, fatigue, emotional and gastrointestinal disturbances, thrombophlebitis, breast soreness, creatinuria, altered serum lipid and lipoprotein levels, thyroid effects, nausea, diarrhea, cramping, weakness, blurred vision, and gonadal dysfunction, but there is an overall lack of consistency among studies as to the types of adverse effects observed (14–16). Whereas selenium is viewed as an antioxidant because of its essentiality for glutathione peroxidase activity, it can also become toxic if ingested in sufficient quantities. Even though the quantity needed to bring about symptoms of chronic selenium intoxication is not known with certainty, gastroenteritis, dermatitis, fatigue, and neurological symptoms such as convulsions, weakness, and decreased cognitive function have been observed (17, 18). In addition, as noted earlier, antioxidants can exhibit prooxidant behavior under some circumstances. For example, one *in vitro* study tested the effects of selenite and SeMet, both commonly used dietary supplements, in combination with either vitamin C, trolox (a water-soluble vitamin E analogue that acts as an antioxidant), or $CuSO_4$ on oxidative damage in the DNA of normal human keratinocytes. Results showed that both vitamin C and $CuSO_4$ protected normal human keratinocytes from selenite-induced DNA damage, and trolox enhanced selenite-induced DNA damage; although SeMet alone did not induce DNA damage, its combination with either trolox or $CuSO_4$ did induce DNA damage (19). Such data suggest that increasing our knowledge about possible prooxidant behavior of some dietary components is needed when evaluating the merits of antioxidants.

Efficacy

Another issue that must be addressed is whether some forms of dietary "antioxidants" are more effective for disease prevention and treatment than others. For example, how do the effects of the form of vitamin E influence the response? Although α-tocopherol is the primary form of vitamin E in tissues, γ-tocopherol, the major form of vitamin E in the United States diet, is well absorbed and also accumulates in some human tissues. In addition to its antioxidant capability, γ-tocopherol inhibits cyclooxygenase activity, has anti-inflammatory properties, and may have still unrecognized benefits for human health. Considering this, should α-tocopherol be used preferentially as a dietary supplement, even though high doses of α-tocopherol deplete plasma and tissue levels of γ-tocopherol (19)? Lycopene, a naturally occurring carotenoid with no provitamin A activity, is found in tomatoes and other red fruits and has been linked epidemiologically with lower incidences of a number of cancers but most strongly with prostate cancer (20). Lycopene has also shown chemopreventive activity in mouse models of cancer (21). It occurs in both all-*trans* and multiple *cis* isomeric forms. All-*trans* lycopene is the primary form found in food, whereas *cis* forms seem to be more readily absorbed from the gut, where isomerization is believed to occur. The *cis* forms are found at the highest levels in tissues (22).

Analytical Issues

When investigating the antioxidative effects of various agents, what are the most appropriate biomarkers of oxidative stress? What are the best ways to measure them? At present, the biomarkers and the methods used to measure them to determine an individual's oxidative status frequently vary among studies, making comparisons of study findings difficult. In addition, the validity of many biomarkers remains to be established. Commonly used biomarkers of oxidative stress include measures of *in vivo* oxidative damage to lipids (*e.g.*, thiobarbituric acid-reactive substances assay, F_2-isoprostanes, and 4-hydroxynonenal), proteins (*e.g.*, protein carbonyl formation), and DNA [*e.g.*, 8OHdG and comet assay for DNA strand breaks (21)]. However, even one of the most widely used methods of assessing DNA damage, measurement of 8OHdG, presents methodological issues. For example, 8OHdG is easily formed as an artifact by oxidation of guanine during DNA isolation, hydrolysis, and analysis (23, 24). This has been extensively investigated using enzymatic and chromatographic (comet and alkaline elution) as well as mass spectrometry coupled with high-performance liquid chromatography (25, 26). Careful method standardization has provided evidence that 0.5 lesion/million bp is a steady-state background level of 8OHdG in lymphocytes (27). Also, 8OHdG can be measured either in cells, where it represents a dynamic equilibrium at the moment of sampling between rates of oxidative DNA damage and rates of repair of that damage, or in urine, where its excretion rate is considered to be an assessment of whole-body DNA damage. Measurement of only urinary excretion, as is done in many studies, may be misleading, because it gives no information about the oxidative steady state (rate of damage *versus* repair) within cells and gives only an average value for damage repair occurring sometime in the past (24, 28). It has been suggested that if only one measurement can be made, the measurement of steady-state DNA damage might be a better predictor of cancer risk because it gives a more real-time assessment (24). The measurement of protein and lipid biomarkers of oxidative stress such as *o*- or *m*-tyrosine, dityrosine, and malondialdehyde or lipid peroxides is less well studied from an analytical standpoint but yields the same concerns. A very informative serial review edited by E. Stadtman (29) covers the subject of oxidatively modified proteins in much more detail than can be discussed here. These uncertainties in the degree and extent of damage are very real and contribute to the "antioxidant conundrum" and are a great impediment to evaluation of the existing data, identification of actual effectiveness, and the development of usage guidelines.

Genetic Variability

Certainly the degree of benefit or harm observed in clinical studies for various antioxidants could depend on genetic susceptibilities, raising questions as to how individual genetic polymorphisms related to the activity of metabolic and detoxification enzymes might influence the effects of antioxidants on *in vivo* redox balance and disease risk. A number of single nucleotide polymorphisms that affect phenotype have been found in genes that code for oxidative stress-related enzymes (30) and base excision repair capacity, (31) with implications for the effects of antioxidants on individual disease susceptibility. For instance, four human single nucleotide polymorphic variants have been reported for manganese superoxide dismutase (32), a nuclear encoded mitochondrial antioxidant protein associated with carcinogenesis inhibition when expressed at higher than normal levels in cell lines (33) and higher tumor incidence in knockout mice in a skin cancer model (34). Another example is the glutathione transferase *GSTM1*-null genotype. This genotype may increase risk for tobacco-related cancers through impaired detoxification of polycyclic aromatic hydrocarbons, which are components of cigarette smoke. Analysis of data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study on lung cancer in male smokers found that, for men in the

highest tertile of smoking (>42 years), vitamin E supplementation was very strongly associated with reduced risk among men with the *GSTM1*-null genotype (odds ratio [OR] = 1.3 *versus* 21.2 with no vitamin E) but much less so compared with men with the *GSTM1* present genotype (OR = 1.3 *versus* 2.4 with no vitamin E; Ref. 35). In another example, data indicated that a codon 399 polymorphism in *XRCC1*, a key gene involved in base excision repair, may modulate the effects of dietary antioxidants on prostate cancer risk. Men homozygous for the 399*Arg* allele of the gene (a common variant), compared with men having either *Arg/Gln* or *Gln/Gln* polymorphisms (combined data), were at higher risk for prostate cancer when dietary intake of either vitamin E (OR = 2.4 *versus* 1.2), vitamin C (OR = 2.3 *versus* 1.4), or lycopene (OR = 2.0 *versus* 1.0) was below the median intake values compared with those patients falling above the median (31). The potential influence of polymorphisms could contribute to the general lack of definitive findings in clinical antioxidant studies and must be considered in future study designs. Perhaps trials in genetic subsets of individuals would yield more definitive data.

Much of the data relating antioxidants to disease risk are observational rather than mechanistic in nature. Under what circumstances do dietary antioxidants affect disease risk through possible mechanisms unrelated to their actions as redox agents, and how might these mechanisms either complement or counteract antioxidant effects? For instance, vitamin E (α-tocopherol) has been reported to modulate cellular signaling, possibly by inhibition of protein kinase C, to regulate gene transcription, to modulate immune function, and to induce apoptosis (36, 37). Recently reported data for rats treated with phenobarbital (a potent tumor promoter) suggested that, at least in this animal model, α-tocopherol can inhibit the activation of nuclear factor κB, a transcription factor that affects gene expression related to cell proliferation and apoptosis (38). A recent study indicates that selenium—as SeMet, reported to be the major component of dietary selenium—regulates the redox state of the *P53* tumor suppressor protein, leading to increased efficiency of DNA excision repair (39). However, selenium has also been reported to modulate immune function, alter carcinogen metabolism and/or carcinogen-DNA binding, suppress cell proliferation, and enhance apoptosis (17, 40–42). Thus, in observational studies of antioxidants, beneficial results may not be solely a result of antioxidant action. Many questions remain to be answered regarding the range of alternative mechanisms through which redox agents might influence disease risk.

Prevention and Therapy Paradigms

It is important to recognize that disease prevention and disease treatment are not identical processes, and it is not logical to assume that the potential effectiveness of antioxidants will be the same in both cases, although the basic mechanisms involved may be similar. Major questions to consider are whether the ROS-related actions and interactions of dietary antioxidants are different in either normal cells or precancerous cells compared with tumor cells, and, if so, whether the differences have significant consequences for using antioxidant supplements combined with standard cancer treatments. Although a reasonable amount of data support a beneficial effect for supplementation with high doses of antioxidants used in combination with conventional cancer therapy (43–47), other evidence indicates that low doses of antioxidants may be detrimental to cancer therapy in many cases (46). Much remains to be learned about the differential effects of antioxidant dose levels, including levels that are "intermediate" between high and low doses. Are there certain cutoff levels for antioxidants where the adverse effects of "low doses" suddenly change to beneficial effects for "high doses?" Or is there a clear linear dose response? Or is there a nonlinear continuum in which beneficial effects gradually outweigh adverse effects as the dose levels of antioxidants increase?

Patient Usage

Many cancer patients take vitamin supplements. For example, a survey of patients at a comprehensive cancer center found that 60% used vitamins, and the majority combined them with conventional therapy (48). Similarly, among a Massachusetts cohort of women with early-stage breast cancer, 60% used megavitamin therapy along with surgery, chemotherapy, and/or radiation therapy (49). Therefore, it is noteworthy that recently reported data from a study in 90 women with unilateral, nonmetastatic breast cancer, who had been prescribed various high-dose combinations of between three and six vitamins and minerals (including vitamin C, β-carotene, selenium, niacin, zinc, and coenzyme Q10) in addition to standard therapies, demonstrated that these women had shorter breast cancer-specific survival time (hazard ratios = 1.75) and disease-free survival time (hazard ratios = 1.55) compared with matched controls (50). Such findings suggest that, until more is known about the effects of antioxidant vitamins in cancer patients, supplementation should be used cautiously, and patients and their physicians should certainly discuss their antioxidant usage.

It is clear that significant gaps exist in the current state of knowledge related to the actions of dietary antioxidants and to the potential advantages and disadvantages of consuming dietary antioxidant supplements, whether they are taken for the equally important purposes of either prevention or treatment. The issues and challenges that are posed by the antioxidant conundrum make this a fertile field for research. A National Cancer Institute-sponsored conference entitled *Free Radicals: The Pros and Cons of Antioxidants*, held on June 26–27, 2003, in Bethesda, Maryland, has been planned to help guide future research efforts.

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