

A Review of Recent Results Addressing the Potential Interactions of Antioxidants with Cancer Drug Therapy

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ABSTRACT

Purpose: Clinical-based hypotheses concerning the consequences of antioxidant uses concurrent with cancer therapeutic interventions range from beneficial to indeterminate to harmful outcomes. Available scientific validity in support of these speculations needs to be examined to clarify the role of antioxidant agents in cancer therapeutic management.

Methods: We reviewed scientific and clinical findings addressing the basis for the primary hypotheses in this area, and identified recent results on antioxidant uses in cancer therapy that help define clinical management issues.

Results: Many hypotheses of speculated harm suffer from absent formal clinical trials evaluation. Other hypotheses are dependent on models of free-radical reduction which are no longer informed models. Available but limited published data are generally not supportive of harmful outcomes, while other data indicate possibly positive adjunctive therapeutic support.

Conclusion: Hypotheses that antioxidants' inhibition of free-radical activity may negate cytotoxic properties of some cancer therapies have been dependent on naive and inaccurate assumptions. The available data suggest a rational basis for the continued use of selected antioxidant agents as therapeutic adjuncts in cancer therapy, with such use also offering a potential to abrogate the carcinogenic process and mutation-driven drug resistance, but convincing data and widespread acceptance of such a role is dependent on additional, appropriately relevant trials.

INTRODUCTION

Extensive controversy surrounds antioxidant compounds' and similar nutrients' protective role against various diseases, including cancer.¹⁻⁴ Recent analyses^{5,6} regarding cancer prevention have held that evidence favors an efficacious role for cancer prevention by certain antioxidants and related vitamin/mineral nutraceuticals in selected carcinomas or for inhibition of the carcinogenic processes in appropriate at-risk populations. In contrast, questions continue to arise whether antioxidants will assist, or conversely, interfere with efficacy of standard cancer treatment approaches. At a clinical level of cancer therapy, this concern has been both advanced and discounted⁷⁻⁹ in recent publications; controversy over the use of large doses of vitamin C as an adjunct to orthodox cancer therapy¹⁰⁻¹² typifies this lack of agreement. In the present review, first we aim to clarify the basis for some of the current scientific and clinical confusion concerning the disparate hypotheses suggesting beneficial, harmful, or indeterminate consequences of antioxidant uses concurrent with cancer therapeutic interventions. Second, to help define the clinical issues, we will identify some recent results of antioxidant uses in cancer therapy and in animal and human tumor models.

ISSUES IN RESEARCH ASSESSMENT

The debate regarding the quality of definitive evidence mandated to prove^{1,13} a protective role of antioxidants in cancer prevention is applicable to an antioxidant's role in cancer therapy per se, or as an adjunct to such therapy. Clinical trials of the role of antioxidants in cancer therapy may face innate limitations since a clinical concern to do no harm may mitigate against their evaluation; cancer prevention trials with all trans beta carotene have shown increased

lung cancer risk with the antioxidant, particularly in smokers.^{14,15} Thus it is not surprising that the available research literature addressing this issue is far from robust, leaving many hypotheses untested or open to strictly theoretical speculation and therefore necessarily leading to a lack of concurrence about the role of antioxidants to modulate the impact of cancer therapy (either positively or negatively). In an effort to clarify these issues, we reviewed all English language articles listed in Index Medicus for the years 1990-2000 that were concerned with antioxidants and related micronutrients with regard to interactions with anticancer drugs or radiation. Further, we examined related issues of antioxidant use in cancer regression and cancer risk.

Confounding Factors

The issue of active antioxidant supplement use in the cancer patient is made complex by data indicating that clinical cancer commonly develops where low plasma and/or tissue levels of antioxidants including vitamin E, ascorbic acid, and the carotenoids including beta carotene are readily demonstrable.^{4,16-23} In the report by Cook et al.,¹⁶ reporting on 14,916 trial subjects from the Physicians' Health Study, there was an increased risk of prostate cancer in those subjects with low baseline serum levels ($p=.07$) with differences between lowest quartiles of serum beta carotene and highest quartiles reflecting major differences in cancer risk. A 17% reduction in total cancer risk and a 32% reduction in prostate cancer risk was seen for the highest quartile of serum beta carotene as compared to the risk for the lowest quartile. Of interest were the serum beta carotene levels of "never" smokers (255 ng/ml), "past" smokers (218 ng/ml), and "current" smokers (172 ng/ml). Further, the clinical cancer population is disproportionately represented by smokers and those who abuse alcohol to varying degrees. These patients frequently have exacerbated antioxidant deficiency often arising from smoking or an antioxidant-deficient diet with decreased plasma levels of certain antioxidants²² not uniformly repleted by dietary and supplement intervention. In smokers, air pollution, exposure to xenobiotics, and activation of drug-metabolizing enzymes may result in low antioxidant serum levels that are not necessarily reflective of their nutritional status.²⁴⁻²⁷ Some patients also have apparently differing biochemical response characteristics to administered antioxidants as compared to cancer patients who do not smoke or consume alcohol.²⁸⁻²⁹

Lack of Therapy Protocols

The role and quantified level of consumed dietary antioxidants by individual patients as contained in fruits, vegetables, and grains, have not been viewed as an issue with respect to a patient's response to anticancer drugs. No specific dietary changes or restorative supplemental nutrients are broadly recommended for the cancer patient per se or as adjuncts for the patient undergoing therapy. Although as noted,^{3,4,16-23} patients' antioxidant plasma levels may be measurably low in a variety of cancerous and pre-cancerous lesions, there is no ongoing clinical practice to correct these deficiencies as part of orthodox anticancer therapies as, for example, physicians might do when faced with low serum sodium, potassium, iron, calcium, or caloric deficiency. Since such antioxidant "deficiency states" could possibly reflect a protective mechanism against cancer growth, as is shown in some tumor models where depleted antioxidant diets lead to increased rates of apoptosis,³⁰ or as was shown in a mouse model genetically programmed to develop breast cancer where an antioxidant-free diet decreased metastases,¹⁴⁶ physicians may theoretically not wish to intervene in this regard in the absence of research data to make an informed intervention. Parenthetically, the noted report³⁰ indicated that a high antioxidant diet had no effect on tumor growth. In another report, cancer cells of mouse tumor models have been shown to have higher levels of vitamin C than normal cells,¹⁰ raising the theoretical question of whether supplemental vitamin C can "feed the tumor." As many cancer patients have diminished food intake because of cancer cachexia syndromes and/or the CNS central and/or local gastrointestinal effects of cancer therapy, antioxidant and vitamin deficiencies may be anticipated to worsen during cancer treatment or disease progression. There is little data on the effects of specific anticancer therapy on baseline levels of micronutrients in the serum. In prevention studies where populations at highest cancer risk will characteristically have the lowest serum and tissue antioxidant levels,^{4,16-27} these deficiencies may often be repleted by antioxidant and dietary supplements, yielding reduced risk in several,^{4,17-23,31-34} if not all, clinical cancers.^{14,15,18,35-41} In the report by Mark et al.³¹ analyzing selenium serum levels as part of the long-term Linxian General Population Trial and focusing on differences between the lowest quartile and highest quartile of selenium levels, the high levels were associated with a 44% reduction of esophageal cancer and a 55% reduction in gastric cardia cancer. Cancer development was seen with mean lower levels of serum selenium for esophageal and gastric cardia cancer but not for antral cancers when compared to controls without cancer. There is further evidence of antioxidants altering the clinical carcinogenic process;⁴² antioxidant use causes regression and complete remission of some pre-malignant lesions.⁴³⁻⁴⁶

In the report by Correa et al.,³² regression of premalignant lesions of the stomach (gastric atrophy or intestinal metaplasia) was seen when treatment was instituted for *H. pylori* infection with antibiotics, or with beta carotene, or with ascorbic acid as compared to controls. There was an 8.7-fold increased rate of regression for atrophic lesions and a 5.4-fold increase in the intestinal metaplasia regression rate in the treatment groups. While each of the three treatment arms did not differ from each other, combinations of treatment further increased the likelihood of regression 3-4 -fold over the single-agent treatment arms. These effects of antioxidants are seen predominantly when results are compared for clinical benefit in those with the lowest serum oxidant levels as contrasted with the highest levels; benefit is most commonly seen in the deficient state.^{16-23,31-34,47} In the instance of smokers however, benefit with beta carotene administration was not seen or was harmful¹⁴⁻¹⁵ with respect to lung cancer risk, while the smoker with low serum levels of alpha tocopherol benefitted with supplement use.^{14,33,48-50} In contrast, beta carotene reduced risk of prostate cancer.¹⁶ The interaction of antioxidant deficiencies with cancer and their modulation by prescribed use of supplements integrated with concomitant cancer therapeutic administration is unfortunately not now an active area of wide interest, nor one with appropriate research support.

Complex Mechanisms of Action

Another potential cause of scientific and clinical confusion surrounding antioxidant use in cancer therapy arises from limited appreciation of the variety and extent of antioxidant drug effects which historically focused on just the immediate intracellular sequelae of free radical and reactive oxygen species scavenging when considering potential beneficial or harmful consequences of antioxidant use. In contrast, more in-depth views, summarized in recent literature pertaining to cardiovascular disease,⁵¹ alone, or more broadly,⁵² of the complex cellular effects of agents with known antioxidant properties, suggest that the issue of benefit versus harm cannot be resolved by focusing solely on an antioxidant's classic mechanistic reduction properties and its attendant impact on free-radical scavenging alone.

THE FREE-RADICAL INHIBITION CONTROVERSY

The potential danger of antioxidant use during cancer therapeutics is argued from recognition that many of the current clinical anticancer drugs induce cellular toxicity and death through mechanisms involving intracellular free-radical generation; it has been theorized that antioxidants, by inhibiting or contradicting intracellular free-radical generation, may then negate aspects of a cancer agent's useful cytotoxic effects.^{7,53-57} Support for such purported antagonism of free-radical damage is complemented by observations where toxic effects of anticancer drugs on normal tissues appear to be prevented or significantly mitigated by a variety of antioxidants.⁵⁸⁻⁶⁰ There is further clinical evidence that antioxidants will protect against and counteract free-radical damage in a variety of normal tissues, such as for ischemic heart damage, in neurologic tissues, as well as in renal, ocular, and other non-cancer, drug-induced normal tissue toxicity.⁶¹⁻⁶⁸ Such antagonism of free-radical normal tissue toxicity has led to speculation about a similar antagonism for anti-cancer drugs' useful effects on tumors. However the experimental evidence for an antagonistic role of antioxidants with respect to the cytotoxic efficacy of anticancer agents is minimal⁵⁴⁻⁵⁸ or directly contradictory,⁶⁹⁻⁷² and, in general, shows considerable variability⁷³⁻⁷⁵ with respect to a specific antioxidant or anticancer agent test in the same model system.

One extension of this concern has been advanced, based on the supposition that one of the multiple, demonstrable factors responsible for inherent or developed tumor cell resistance to anticancer drug therapy is intracellular levels of superoxide dismutases. Manganese dismutase (MnSOD) has been studied most and is the predominant intracellular dismutase, but other metal ion dismutases (e.g., Cu-ZnSOD), catalases, and glutathione peroxidases are also known important inhibitors of intracellular free radicals and superoxide species. The anticipated effects of MnSOD are in reducing intracellular oxidative stress, thereby decreasing the potential for DNA damage, carcinogenesis,⁷⁶ and free-radical-induced cytotoxicity.^{53,77,78} Patients with high tumor cell levels of MnSOD (and possibly resulting reduced free-radical species) may have a shorter survival than those with low levels⁷⁹ together with a variety of features indicating aggressive tumor phenotype.^{80,81} Tumors with primary and/or secondary resistance to chemotherapy^{53,78} and hormonal therapy⁸² will often demonstrate high levels of MnSOD; as high or induced levels of MnSOD could limit free-radical persistence, and thus the cytotoxicity of anticancer drugs⁵³ such as mitomycin-c, bleomycin, adriamycin, and others, so too could anticancer effects be minimized if oxidant cellular defense mechanisms modulated by MnSOD were further augmented by antioxidants. However, in vitro studies have indicated that intracellular catalase activity and glutathione metabolism may be more important variables⁸³⁻⁸⁵ in cancer-induced cell toxicity than MnSOD with anticancer drug-mediated cytotoxicity at times being shown to be unrelated directly to

MnSOD levels⁸⁰ in some models. Further studies with a variety of antioxidants that complement intracellular oxidative defense mechanisms have shown paradoxical potentiation of free-radical species-induced DNA and lipid membrane damage.⁷³⁻⁷⁵

The view that antioxidants' preventative role in free-radical formation may be an antagonist to the goal of free-radical formation by cytotoxic drugs is further challenged by other recent research. In both tissue culture and a variety of animal model systems, substances such as vitamin E, carotenoids, and ascorbic acid, viewed classically as antioxidants, have often been shown to be antioxidants in certain systems and pro-oxidants in others, depending on the system studied and the dosages explored; in differing studies, one can demonstrate both antioxidant and pro-oxidant intracellular effects of a wide variety of putative antioxidants.⁸⁶⁻⁹⁷ In some instances, the pro-oxidant effects of these agents will influence intracellular levels of glutathione, often converting reduced glutathione (GSH) to oxidized glutathione (GSSH) and removing thereby important intracellular defense mechanisms against cytotoxic agents such as commonly used chemotherapy. In other instances intracellular oxidation products of antioxidants⁹⁶ often generated by interaction with H₂O₂^{70,98} enhance drug cytotoxicity or promote apoptosis and will have important oxidative DNA damaging effects in tumor systems and normal tissues; these effects may be concentration-dependent.⁹³ Such results indicate that the notion of antioxidant versus pro-oxidant drug action must be viewed with respect to their actions being concentration-dependent,^{28,74,90,93} sequence-dependent,⁹⁸ and/or may vary depending on the target markers measured.^{54,56} Experimental data with ascorbic acid typifies this dichotomy of antitumor effects with antioxidants. While in some systems ascorbic acid will antagonize apoptosis and some antiproliferative drug effects,¹⁴⁷⁻¹⁵⁰ when combined with the clinically useful anticancer drug arsenic trioxide (Ar2O3), ascorbic acid enhances antitumor effects in Ar2O3-resistant murine tumor cell lines and in vivo, at ascorbic acid doses of 500 mg/kg without increased normal tissue toxicity.⁸⁶ These potentially clinically relevant data with adjunctive use of ascorbic acid have been further addressed recently for application to clinical acute leukemia.¹⁵¹ Therefore a distinction a priori cannot be accurately made for a compound's pro-oxidant or antioxidant effects on cellular systems relevant to cancer therapy without reference to the clinical or experimental situation for tumors, or for limited or contrasting effects on normal tissues, or with specific anticancer drugs.^{6,99}

Similarly in other assay systems, antioxidant compounds have demonstrated a variety of other useful anticancer effects, particularly in induction of malignant cell apoptosis.¹⁰¹⁻¹⁰⁷ Table 1 lists some other non-antioxidant-based effects of those compounds recognized largely heretofore for their antioxidant properties. Such anticancer effects of antioxidant compounds are expressed via enzymatic and activation pathways, may modulate gene expression, and influence cellular proliferation pathways in ways other than necessarily directly dependent on free-radical activation and/or persistence; it is recognized that perturbations in redox systems by "antioxidant" compounds may lead to some of the noted effects secondarily.⁷⁶ However, in most instances these effects are demonstrably "non-antioxidative" and are readily separable experimentally: for vitamin E, for example, several tocopherols exhibit non-antioxidant effects and are known to be free of antioxidative function. Such evidence argues for a useful interplay between these compounds with pro-antioxidant, antioxidant, and non-antioxidant properties and recognized anticancer agents. Here, too, there is need for caution in that pro-oxidant/antioxidant drugs could influence intracellular release of those intracellular transition metal ions which are themselves catalysts of oxidative damage and which could enhance cytotoxic drug effects, or potentially inhibit progression of apoptosis and lead to cellular necrosis with important secondary growth factor tumor stimulation by attracted mononuclear cell infiltrates.

CLINICAL IMPLICATIONS AND EXTENDED OBSERVATIONS

Of note, the National Institute of Medicine recommendations for daily recommended (RDA) and upper tolerable levels (UTL) of intake of antioxidants and vitamins have recently increased (Table 2) for the normal American diet in people without disease. Antioxidant compounds have been extensively used to reduce drug-induced clinical toxicity in cancer patients; decreased therapeutic efficacy has not been observed, for example, in the cases of the use of agents Amifostine (with cisplatin), Mesna (with Ifosphomide), and Dextrazone (with Adriamycin), which are now standard in clinical oncology practice.¹²⁷⁻¹²⁹ A recent review reflecting a broad range of antioxidant clinical effects in the cancer patient echoes the useful potential of these adjunctive agents.¹³⁰ The few recent clinical trials of standard cancer therapy with concomitant antioxidants have not noted diminished antitumor effects. In some trials, multiple antioxidants have been combined,¹³¹⁻¹³⁴ paralleling positive results in prior and planned prevention studies. For example, Propax[®], a novel proprietary phosphoglycolipid in nutrient complexes, has been employed clinically to increase multi-antioxidant cellular drug delivery and has demonstrated clinical usefulness in early trials in cancer

patients undergoing chemotherapy.¹³⁵ The research of Helzlsouer et al.⁵⁰ bears testimony to the potential efficacy of antioxidant combinations. The study showed an increased risk of prostate cancer in patients with lower serum selenium levels than controls; the presence of high serum gamma tocopherol levels yielded a five-fold reduction of cancer risk for patients with high selenium levels as compared to lowest levels. Serum gamma tocopherol above the 50% median level of control patients, coupled with selenium and alpha tocopherol levels similarly high, resulted in a 50% reduction in cancer risk. In vitro studies support the potential for synergistic cytotoxic effects in cancer cell lines with the use of antioxidant combinations.^{72,100,112}

Of additional recent clinical interest is experimental data that Tamoxifen resistance in breast cancer cells is associated with oxidative stress,¹³⁶ and, separately, that vitamin E by trapping electrophils resulting from oxidative damage will inhibit neutrophil infiltration into tumor and normal tissue¹³⁷ as well as inhibit endothelial adhesion. As macrophage and neutrophil infiltration with attendant cytokine growth factor elaboration may be contravened by such anti-inflammatory effects of vitamin E, new avenues for research in antioxidant drug effects on tumors¹³⁸⁻¹⁴⁰ is readily evident. The established interaction of genetic susceptibility to cancer,¹⁴¹⁻¹⁴³ and the modulation of progressive tumor mutation recently demonstrated again with antioxidants¹³⁷ as distinct from their modulation of normal tissue mutation rates,¹⁴⁴ also offer useful promise in favorably influencing cancer cell resistance to therapy, a process usually reflective of progressive tumor mutational change. Recent work by Hamada et al.¹⁴⁵ demonstrated that epidermal growth factor (EGF) can stimulate oxidative DNA damage in vitro in a mammary tumor cell line. However, treatment with EGF but with added N-acetylcystein or selenium will reduce elevated intracellular levels of peroxidase and 8-hydroxydeoxyguanosine and prevent in vivo tumor invasiveness, metastatic ability, and rate of tumor formation, all effects of EGF when used alone. While there is reason for cautious optimism in the use of "antioxidants" at clinical tolerable doses during cancer therapy, data still are not definitive regarding favorable consequential side-effects of higher dose levels on specific cancer disease states.

SUMMARY

Assessing the role of antioxidants in cancer therapy has been shown to be substantially far more complex than researchers and clinicians initially anticipated, with many initial hypotheses contingent on naive or inaccurate assumptions. Among the most considered hypotheses relating to adverse effects of antioxidants in cancer therapy has been speculation that antioxidants' inhibition of free-radical activity may negate cytotoxic properties of some cancer therapies. Testing of this hypothesis has suffered from remarkably absent formal clinical trials evaluation. More recent expositions of antioxidants' actions lead to the recognition that the basis of the hypothesis' supposition, dependent as it is on the simple notion of free-radical reduction, is no longer an informed model. Recent clinical and laboratory evidence is supportive of an evolving model that a pro-oxidative/antioxidative/non-antioxidant assessment of a drug's effects is more appropriate and needs to be applied to specific situations, marker systems, and modulated by host factors. This review suggests there is a rational basis for the continued use of antioxidant agents as a therapeutic adjunct in cancer therapy. Such use also offers a potential to abrogate the carcinogenic process and mutation-driven drug resistance. However, convincing assessment and widespread acceptance (or rejection) of such a role for these agents will accrue only with additional, clinically-relevant, prospective placebo-controlled randomized trials in combination with careful monitoring of antioxidant use.

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Table 1. Some Non-Antioxidant Properties of Common "Antioxidants"
ANTIOXIDANT and REFERENCE
Retinoic Acid Derivative
Exhibits anti-angiogenic properties ¹⁰¹
Induces metalloprotease-1 gene expression ¹⁰⁸
Down-regulates insulin like growth factor binding proteins ¹⁰⁹
Inhibits IGF-1, ODC ³
Induces TGF beta ³
Inhibits telomerase ³
Inhibits thrombomodulin ³
Increases connexin ³
Induces osteopontin expression ¹¹⁰
Vitamins C and/or E

Inhibits androgen induced AP-1 and NF-KB DNA binding sites (transcriptional activators) ¹¹¹
Induces apoptosis ^{102, 112-114}
Activates calcineurin (protein phosphatase 2B) ¹¹⁵
Inhibits protein kinase C ¹¹⁶
Carotenoids
Inhibits or regulates gene expression on connexins ^{117, 118}
Produces pro-and anti-carcinogenesis ^{95, 119}
Enhances cell transforming activity ⁹²
Suppresses RAR-beta and increase activator protein-1 ¹¹⁹ Induces TGF beta ³
Inhibits carcinogen induced neoplastic transformation ¹¹⁹
Ebselen (2-phenyl-1, 2-Benzisoselenazol-3(2H)-one)
Induces apoptosis through depletion of intracellular thiols ¹⁰³
Melatonin
Induces apoptosis in EAC cells ¹⁰⁴
Regulates sleep-wake cycle ¹²⁰
Regulates gluco-corticoid receptor ¹²¹
Blocks activation of estrogen receptor for DNA ¹²²
Reversatrol
Induces apoptosis in HL-60 cells ¹⁰⁵
Quercetin
Induces apoptosis in colorectal tumor cells ¹⁰⁶
PDTC (Pyrrolidine dithiocarbamate)
Induces apoptosis by raising redox-active copper ⁹⁷
Induces apoptosis by cytochrome C dependent mechanism ¹⁰⁷
Affects binding of NF Kappa B to DNA ¹²³
Silibinin and Other Flavonoids
Induces G-cell arrest in prostate cancer cells ¹²⁴
Induces p53-independent apoptosis ¹²⁵
PDTC and Vitamin E
Induces apoptosis in CRL cells by induction of p21WAF1/Cip1 inhibition of cell cycle ¹⁰⁵
Polyphenols
Induces G ₂ /M phase cell arrest in PC-3 tumor cells ¹²⁶
Table 1. Some Non-Antioxidant Properties of Common “Antioxidants”

Table 2. New Recommended Daily Vitamin Intake*		
Daily Dietary Recommended Allowance		
Vitamin C male	90 mg	
Vitamin C female	75 mg	
Vitamin E	15 mg	
Selenium	15 mg	

* Institute of Medicine, National Academy of Sciences, Food and Nutrition Board, Panel on Dietary Antioxidants and Related Compounds. Dietary reference intakes for vitamin C, vitamin E, selenium and Carotenoids. Washington DC: National Academy Press: 2000

Table 2. New Recommended Daily Vitamin Intake*