REVIEW ARTICLE

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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.

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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 discounted[7-9] in recent publications; controversy over

the use of large doses of vitamin C as an adjunct to orthodox cancer therapy[10-12] 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,[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 antioxidants[22] 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 report[30] 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

levels of MnSOD (and possibly resulting reduced free-radical species) may have a shorter survival than those with low levels[79] 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 therapy[82] 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 drugs[53] 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 variables[83-85] in cancer-induced cell toxicity than MnSOD with anticancer drug-mediated cytotoxicity at times being shown to be unrelated directly to MnSOD levels[80] in some models. Further studies with a variety of antioxidants that complement intra-cellular 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 antioxidants[96] often generated by interaction with H_2O_2[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 (Ar_2O_3), ascorbic acid enhances antitumor effects in Ar_2O_3-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 Medi-cine 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),

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.ODC3 Induces TGF beta[3]
Inhibits telemerase[3]
Inhibits thrombomodulin[3]
Increases connexin[3] Induces osteopondin expression[110]
Vitamins C and/or E
Inhibits androgen induced AP-1 and NF-KB DNA binding sites (transcriptional activators)"[1]
Induces apoptosis[102-112-114]
Activates calcineurin (protein phosphatase 2B)[115]
Inhibits protein kinase C [116]
Carotenoids
Inhibits or regulates gene expression of connexins[117,118]
Produces pro-and anti-carcinogenesis[95-119]
Enhances cell transforming activity[92]
Suppresses RAR-beta and increase activator protein-I[119]
Induces TGF beta[3]
Inhibits carcinogen induced neoplastic transformation[119]
Ebselen (2-phenyI-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]
Resveratrol
Induces apoptosis in HL-60 cells[105]
Quercetin
Induces apoptosis in colorectal tumor cells[106]
PDTC (Pyrrollidine 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 Flavoiioids
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 p21WAFl/CIPl inhibition of cell cycle[105]
Polyphenols
Induces G2/M phase cell arrest in PC-3 tumor cells[126]

Mesna (with Ifosphomide), and Dextrazazone (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 anti-oxidants 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 tissue[137] 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 tumors[138-140] is readily evident. The established interaction of genetic susceptibility to cancer,[141-143] and the modulation of progressive tumor mutation recently demonstracted again with antioxidants[137] as distinct from their modulation of normal mutation rates,[144] also offer useful promise in favorable influencing cancer cell resistance to therapy, a process usually relective of progressive tumor mutation 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.

Table 2. New Recommended Daily Vitamin Intake*

		Recommended Daily Dietary Allowance	Upper Daily Tolerable Level
Vitamin C	male	90 mg	2000 mg
	female	75 mg	2000 mg
Vitamin E		15 mg	1000 mg
Selenium		55 micrograms	400 micrograms

*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

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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