

Antioxidants and Cancer: A Brief Discussion on Controversies, Contradictions and Paradoxes

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Abstract

Antioxidants have been associated with cancer prevention. Since this association was established, a plethora of controversies, contradictions and paradoxes have arisen. In this article we will try to provide an insight into the complexity involved with antioxidants, pro-oxidants and cancer in the free radical biology area.

Introduction

A report by Hunter et al.¹ studying antioxidant intake and the risk of breast cancer, using as study cohort a large number of female registered nurses, found no protective effect of large intakes of vitamin C or E and only a slight benefit of vitamin A intake was found and limited to women with low vitamin A intakes. This report has been used as a negative argument against the use of antioxidant chemoprevention.

Another highly publicized study the Finnish antioxidant and lung cancer study² also failed to detect a preventive action of high dose antioxidants. In this study Finnish smokers supplemented with synthetic beta-carotene (20 mg ± 33,000 IU/day) developed lung cancer at significantly higher rate (18%) than those utilizing a placebo. Lung cancer incidence in smokers taking synthetic vitamin E (50 mg or 50 IU of dl-alpha-tocopherol acetate) or both beta-carotene and vitamin E was not significantly different from those taking a placebo. Incidence of other cancer was only minimally affected except for a positive effect of vitamin E on prostate and

colorectal cancer. The authors stated that their results have not been consistent with many previously published studies.

These contradictory results are surprising since many previous studies have shown a protective effect of various antioxidants against various types of cancers. Moreover, epidemiological evidence exists linking high intake of vegetables rich in carotenes with significantly lower risk of cancer, especially lung cancer.^{4,5}

Greenberg et al³ reported a lack of preventive action of antioxidants in a clinical intervention trial in which several antioxidants (beta carotene and/or vitamins C and E) were used as chemopreventive agents against colorectal adenomas.

As scientists it is our obligation to analyze these seemingly unexplicable controversies. Why these totally opposed findings? We have to take careful consideration of confounding factors that could help us find possible explanations for these opposed findings.

It should be pointed out as a reply to the Hunter et al. study that in many occasions the range of nutrient intake in human diet may not be above the threshold at which a protective effect of the antioxidants can be expected. Also, inverse associations between antioxidant intake and cancer risk can only be detected in a population if the difference between the group of the highest intake and the group of the lowest intake is sufficiently large. Homogenous populations used in some of these studies tend to consume similar diets, having more or less similar dietary intakes of antioxidants. These result in narrow ranges of serum antioxidants. Interestingly even with these narrow ranges the majority of studies have found a significant inverse

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association between antioxidants and risk of cancer.⁶⁻¹⁰ Nevertheless these studies did not receive much public attention.

In relation the Finnish antioxidant and lung cancer study,² the first issue relevant to this study is the form of supplement that was administered. The synthetic beta carotene contained other ingredients (these ingredients were not mentioned in the papers). It is not clear if the placebo also contained these ingredients. The vitamin E form used was a synthetic alpha tocopherol/acetate form which in some animals models has increased tumor growth.¹¹ In contrast, another form of vitamin E, tocopherol succinate has shown a suppressive potential against tumor growth.¹²

Another important issue is the low dosage of individual antioxidants used in this study, only $1/8$ to $1/40$ of the intake used in previous studies. Low doses of multiple vitamins (but not individual ones) have reduced the risk of cancer.¹³ Also among the placebo groups the authors divided vitamin E and B-carotene levels into lowest and highest quartile groups which showed a protective effect of these nutrients. Surprisingly, the authors did not make such analysis among experimental groups.

The vitamin E group had an insignificant 2% reduction in the incidence of lung cancer. The beta carotene supplemented group had an 18% increase in incidence. While an 18% increase is statistically significant it can be biologically irrelevant. The reasoning here is as follows: out of the 14,560 men on beta carotene, 474 developed lung cancer while of the 14,573 men on placebo, 402 developed lung cancer. The incidence increased from 2.76% for the control group and 3.26% for the treated group. This 0.5% difference becomes 18% difference when you divide 3.26 by 2.76¹⁹ which was the distorted value focused by the media. In a large population study like this, the possibility of only a minor variation will enable this type of misinterpretation.

Another important point is the duration of the supplementation which might have been short (just six years after smoking \pm a pack of cigarettes a day for 35 years). Interestingly overall mortality from cerebrovascular disease was reduced by 10% in subjects receiving antioxidant and overall mortality was also reduced 7% in the supplemented group.

Also the authors should have considered the additional risk factors (such as alcohol consumption) in the Finnish people that skews cross-cultural comparisons and questions the appropriateness of this population for this type of study. Most of these same issues apply to the Greenberg study as detailed by Leibovitz elsewhere.¹⁵

Most studies with antioxidants suggest that their chemopreventive action is associated more closely with early initiation and promotion stages of carcinogenesis.

Nevertheless we should have in mind that in some in vitro tests indicate the possibility that high doses of single antioxidants in the presence of low levels of other micronutrients and high oxidative stress states can result in cell injury.

Also beta carotene works well at low partial pressure.¹⁰ It is very likely that in the lungs of smokers, different oxygen pressures exist. This, in addition to a concentration of any of chemicals, may disrupt beta carotene preventive capacity. If a combination of antioxidants which have demonstrated sparing and potentiation activity¹⁷ were used, it would have been of great interest to observe. Nevertheless it is conceivable that the cancer preventive capacity of antioxidant nutrients may be due to their pro-oxidant potential since studies by González et al.¹⁸ and Tsao et al.¹⁹ have pointed toward this possibility.

What we can conclude from this study is that beta carotene taken at a low dose for relatively short time in the absence of other nutrients and a healthy lifestyle may not prevent lung cancer in heavy smokers. This issue is of such complexity that clini-

cal trails alone cannot give a total unequivocal answer. We need to carefully examine the totality of the evidence (experimental, epidemiological and clinical) combined with sound scientific judgement to effectively answer if antioxidants can be regarded as cancer chemopreventive agents.

Another issue we should mention is a biphasic action of antioxidants (such as tocopherol). Alpha tocopherol shows a distinct concentration of optimum antioxidant effectiveness above which its effectiveness declines and becomes strongly pro-oxidant.²⁰ Also ascorbic acid (vitamin C), an aqueous antioxidant, regenerates tocopherol²¹ but behaves as a pro-oxidant in the presence of transition metals.²² These examples of paradoxical reductive promotion of oxidation have been reported in vitro, but whether these reactions occur in vivo is not clear. Although it has been reported that antioxidants inhibit normal cells from becoming transformed, antioxidants also inhibit the growth of already transformed cells through their pro-oxidant activity.²³

It is interesting how many of these actions may be controlled by the redox status of cells that, if shifted toward the oxidative side, a cell may go from quiescent to extremely proliferative. If the oxidative stress is intensive rather than transient the proliferative state may be perpetually sustained, becoming a malignant cell. If this oxidative shift can be of such great magnitude that cellular mechanisms may not be able to survive and the cell will die.

Sadly, there is no black and white answer to this problem. Oxygen intermediates are capable of inflicting severe damage to cells that may even lead to their death. At the same time, these species may serve as important physiological signals and may play vital protective roles in the cell metabolism. It all depends on where, when, what and how much is produced that can determine what will happen to a cell in a specific moment. This is why free radical

biology (antioxidants and pro-oxidants) can seem conflicted, controversial and contradictory, but nevertheless fascinating!

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