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Editorial

Antioxidant Supplementation: Revisited

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The rationale upon which antioxidant research has been based rests with the assertion that oxidants assault and degrade biological molecules, either genetic or epigenetic, resulting in aging, cancer, or specific disorders that can be directly related to oxidant insult. This is the essence of Harman's "Free Radical Theory of Disease" [1]. It was a logical step to recommend that the addition of one or more antioxidants to ones diet could assuage free radical damage and thus reduce cancer risk. Subsequently, an international multi-billion dollar industry in dietary supplements has evolved, with a large fraction being antioxidants. Most of these supplements are of natural origin and, thus, their use is unregulated and often untested for safety. However, it must be recognized that under certain conditions, an antioxidant may act as a pro-oxidant, and even though a substance may act as an antioxidant, its action may be rather specific in specific tissues and the overall effect may not be anticipated. As an example, butylated hydroxytoleune (BHT) appears to be an effective inhibitor of UV-carcinogenesis, but it, like any other chemical introduced into biological systems produces other physiological effects. BHT has been reported to act as a tumor promoter under certain protocols. It also induces hepatomegealy and hepatic Phase I and II microsomal detoxification enzymes that may predispose the host to chemical carcinogenesis [2].

Another example of an antioxidant exhibiting pro-cancer effects is that of β-carotene. β-carotene is one of about 100 carotenoids that are found in human foods. It is an important micronutrient, functioning as the precursor for vitamin A synthesis. It also is an efficient singlet oxygen quencher and, under certain conditions, is an effective antioxidant. However, under increased oxygen tension it acts as a pro-oxidant. An epidemiological study examining the intake of green leafy vegetables found an inverse relationship between greater intake and cancer risk [3]. As these foods are rich in β-carotene, and β-carotene is an efficient singlet oxygen quencher, the carotenoid was singled-out for further examination and it was found that human cancer risks were inversely correlated with dietary β-carotene intake. β-carotene had been shown to inhibit UV-carcinogenesis [4] but recent studies found that under some dietary conditions it exacerbated UV-carcinogenesis [5]. The role of β-carotene as an anti-cancer agent began to be questioned when a clinical intervention trial failed to find a reduction of non-melanoma skin cancer (NMSC) occurrence in those NMSC patients treated with β-carotene supplements over a five year period [6]. But more significantly, β-carotene supplemented male smokers suffered a significant increase in lung cancer occurrence [7]. Thus, while β-carotene is an important micronutrient for maintenance of good health, supplementation with this carotenoid as a mean to reduce cancer risk is fraught with hazard. Indeed, the IARC [8] concluded "*Until further insight is gained, ß-carotene should not be recommended for use in cancer prevention in the general population and it should not be assumed that ß-carotene is responsible for the cancer protecting effects of diets rich in carotenoid containing fruits and vegetables".*

Conflicts in the literature regarding the benefits and risks of antioxidant supplementation provide no clear recommendations for the general public to follow. One recent meta-analysis study, although controversial, concluded that vitamins A and E, and β-carotene supplementation might increase the mortality risk from all causes by as much as 16% [9]. A second study found no statistically significant association of vitamin/mineral supplementation with cancer, cardiovascular, or all cause mortality [10]. These investigators did observe, however, that baseline users of antioxidant vitamin supplements (those who were already taking supplements at baseline of the study) had a significantly reduced risk of cancer mortality (48%) and all cause mortality (42%) compared to those who only began supplementation at baseline. It was suggested that the increased risk of cancer and all cause mortality among those who just began supplementation at baseline might be due to a "sick-user effect" and demonstrated that timing of antioxidant supplementation is a factor that can influence response and cloud results from observational studies. These types of uncertainties, coupled with the experimental *in vivo* factors impacting antioxidant efficiency, e.g., target tissue absorption and concentrations; rate constants for radical reactions *in vivo*; turnover rates in the target tissue; rate of regeneration or recycling, illustrate some of the complexities that must be considered when supplementing the diet with antioxidants. These complexities are compounded when antioxidants interact with other agents and has led to a broad controversy regarding antioxidant supplementation during cancer chemo and radiation therapy. It may be necessary to develop an algorithm for each antioxidants supplement based upon the benefit to be derived for a specific cancer and the potential risks to each individual for other forms of cancer and all cause mortality. Antioxidant supplementation of the complex and intricately balanced natural antioxidant defense system with what, under controlled physiochemical conditions are efficient antioxidants, all with the intention of limiting free radical mediated damage, is a course of disease prevention not without risk. This has led the World Cancer Research Fund/American Institute for Cancer Research [11] to state "*A general recommendation to consume supplements for cancer prevention might have unexpected adverse effects"* and thus *"Dietary supplements are not recommended for cancer prevention".*

Until we have answers to some of the concerns surrounding antioxidant supplementation, the best recommendation for maintaining a strong antioxidant defensive system may be the consumption of a balanced diet containing adequate green leafy and yellow vegetables that are known to be rich in a broad range of antioxidants and from which the original observations of reduced cancer risks were based.

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