



In the News!

Charles H. Taylor, MD – January, 2003



ANTIOXIDANTS and OTHER PHYTOCHEMICALS: Current Scientific Perspective

Many "antioxidant" products are marketed with claims that, by blocking the action of free radicals, they can help prevent heart disease, cancer, and various other conditions associated with aging.

Free radicals are atoms or groups of atoms that have at least one unpaired electron, which makes them highly reactive. Free radicals promote beneficial oxidation that produces energy and kills bacterial invaders. In excess, however, they produce harmful oxidation that can damage cell membranes and cell contents. It is known that people who eat adequate amounts of fruits and vegetables high in antioxidants have a lower incidence of cardiovascular disease, certain cancers, and cataracts. Fruits and vegetables are rich in antioxidants, but it is not known which dietary factors are responsible for the beneficial effects. Each plant contains hundreds of phytochemicals (plant chemicals) whose presence is dictated by hereditary factors. Only well-designed long-term research can determine whether any of these chemicals, taken in a pill, would be useful for preventing any disease.

The most publicized phytochemicals with antioxidant properties have been vitamin C, vitamin E, and beta-carotene (which the body converts into vitamin A). Evidence exists that vitamin E can help prevent atherosclerosis by interfering with the oxidation of low-density lipoproteins (LDL), a factor associated with increased risk of heart disease.

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However, vitamin E also has an anticoagulant effect that can promote excessive bleeding. In 1993, *The New England Journal of Medicine* published two epidemiologic studies which found that people who took vitamin E supplements had fewer deaths from heart disease [1,2]. These studies did not prove that taking vitamin E was useful because they did not rule out the effects of other lifestyle factors or consider death rates from other diseases. Moreover, other studies have had conflicting results. The only way to settle the question scientifically is to conduct long-term double-blind clinical studies comparing vitamin users to nonusers and checking death rates from all causes.

At least seven large clinical trials have been reported. The first trial compared the effects of vitamin E (alpha-tocopherol), beta-carotene, and a placebo among heavy smokers. The researchers found no benefit from vitamin E and 18% more lung cancer among those who received beta-carotene. In addition, the overall death rate of beta-carotene recipients was 8% higher, and those who took vitamin E had a higher frequency of hemorrhagic stroke [3]. In 1997, the researchers reported on the effect of vitamin E or beta-carotene on the incidence of heart attacks or death among the subjects who had had a previous heart attack (myocardial infarction). The report covered 1,862 men aged 50 to 69 who were followed for a median of 5.3 years. The men had received dietary supplements of alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both, or a placebo. There were significantly more deaths from coronary heart disease among those who took beta-carotene supplements, and a trend toward more deaths (but not enough to be statistically significant) in the vitamin E group [4].

The second study found no evidence that supplementing with vitamin C, vitamin E, or beta-carotene prevented colorectal cancer [5]. The third study, which followed 22,000 physicians for 12 years, found no difference in cancer or cardiovascular disease rates between users and nonusers of beta-carotene [6]. The fourth trial, which tested a combination of beta-carotene and vitamin A, was terminated after four years because it appeared that the supplement-takers who smoked had a 28% higher incidence of lung cancer and a 17% higher death rate [7].

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More recently, a double-blind clinical trial found that taking high doses of vitamins C and E and beta-carotene did not reduce the odds of arteries reclogging after balloon coronary angioplasty. The patients took either probucol (a cholesterol-lowering drug), probucol plus the three antioxidants, the antioxidants alone, or a placebo. More than 200 patients completed the study without protocol violations. Patients in the antioxidant groups received 30,000 IU of beta-carotene, 500 mg of vitamin C, and 700 IU of vitamin E twice daily. All of the patients received aspirin, which is known to reduce the incidence of reclogging. After six months, the rates of repeated angioplasty were 11% in the probucol group, 16.2% in the combined treatment group, 24.4% in the multivitamin group, and 26.6% in the placebo group [8].

Another study involved 2,545 women and 6,996 men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor. These patients were randomly assigned to receive either 400 IU of natural vitamin E or a matching placebo for an average of 4.5 years. There were no significant differences in heart attacks, strokes, or death between the vitamin E and placebo groups. The researchers concluded that "In patients at high risk for cardiovascular events, treatment with vitamin E for a mean of 4.5 years has no apparent effect on cardiovascular outcomes." [9]

Yet another study tested aspirin, vitamin E, and beta-carotene in the prevention of cancer and cardiovascular disease among 39,876 women aged 45 years or older. Among those randomly assigned to receive 50 mg of beta-carotene or a placebo every other day, there were no statistically significant differences in incidence of cancer, cardiovascular disease, or overall death rate after a median of two years of treatment and two years of follow-up [10].

Charles Hennekens, M.D., a who participated in two of the above studies, has pointed out that even if antioxidants could provide the benefits suggested by epidemiologic studies, smoking cessation and other lifestyle factors would have a far greater effect on the rates of lung cancer and coronary heart disease [11]. *The Medical Letter* has concluded:

- The benefits of taking high doses of vitamin E remain to be established.
- There is no convincing evidence that taking supplements of vitamin C prevents any disease.
- No one should take beta carotene supplements [12].

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The American Heart Association's nutrition committee has issued a science advisory discussing relationships between antioxidants and heart disease. The statement concludes:

Considerable evidence now suggests that oxidants are involved in the development and clinical expression of coronary heart disease and that antioxidants may contribute to disease resistance. Consistent with this view is epidemiological evidence indicating that greater antioxidant intake is associated with lower disease risk. Although this increased antioxidant intake generally has involved increased consumption of antioxidant-rich foods, some recent observational studies have suggested the importance of levels of vitamin E intake achievable only by supplementation. There is currently no such evidence from primary prevention trials, but results from secondary prevention trials have shown beneficial effects of vitamin E supplements on some disease end points. In contrast, trials directly addressing the effects of beta-carotene supplements have not shown beneficial effects, and some have suggested deleterious effects, particularly in high-risk population subgroups.

In view of these findings, the most prudent and scientifically supportable recommendation for the general population is to consume a balanced diet with emphasis on antioxidant-rich fruits and vegetables and whole grains. This advice, which is consistent with the current dietary guidelines of the American Heart Association, considers the role of the total diet in influencing disease risk. Although diet alone may not provide the levels of vitamin E intake that have been associated with the lowest risk in a few observational studies, the absence of efficacy and safety data from randomized trials precludes the establishment of population-wide recommendations regarding vitamin E supplementation. In the case of secondary prevention [protection of people known to have coronary artery disease], the results from clinical trials of vitamin E have been encouraging, and if further studies confirm these findings, consideration of the merits of vitamin E supplementation in individuals with cardiovascular disease would be warranted. [13]

Research is also being done to determine whether taking supplements or eating foods rich in antioxidants can protect against age-related macular degeneration (AMD), a disease in which the central portion of the retina deteriorates so that only peripheral vision remains.

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A team of Australian researchers who followed 3,654 subjects age 49 or older found no statistically significant association between AMD and dietary intake of either carotene, zinc, or vitamins A or C, either from diet, supplements, or both [14]. Other published studies have had conflicting results, with some finding correlations and others finding none [14].

The key question is whether supplementation with antioxidants (or other phytochemicals) has been proven to do more good than harm. The answer is no, which is why the FDA will not permit any of these substances to be labeled or marketed with claims that they can prevent disease.

The negative publicity has not deterred manufacturers from continuing to market antioxidants as though they have been proven beneficial. Many have also responded by hyping new mixtures of beta-carotene and other carotenoids, which, they suggest, may provide the same benefits as fruits and vegetables.

Many types of pills described as "concentrates" of fruits and/or vegetables are being marketed. However, it is not possible to condense large amounts of produce into a pill without losing fiber, nutrients, and many other phytochemicals [15]. Although some products contain significant amounts of nutrients, these nutrients are readily obtainable at lower cost from foods.

Researchers at the Jean Mayer USDA Human Nutrition Research Center at Tufts University have completed a study that may explain why very high doses of beta-carotene appeared to increase lung cancer rates among smokers in the 1994 and 1996 studies noted above. The study was conducted in ferrets, which metabolize beta-carotene much like humans. The researchers found that excess amounts stored in the lungs became oxidized into substances that decreased a tumor suppressor and increased a tumor promoter in the animals' lungs. The ferrets were divided into four groups. One received beta-carotene and was exposed to cigarette smoke equivalent to a human smoking 1.5 packs per day. Two other groups got either the supplement or smoke exposure, and a control group got neither. The first group had the strongest precancerous changes [16].

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A 1-year study of 153 patients has found that supplements of vitamin C, vitamin E, beta-carotene and selenium may interfere with the ability of simvastatin (Zocor) and niacin to raise the HDL levels of patients with abnormally low HDL levels. The patients receiving antioxidants and drugs had an average HDL increase of 18%, whereas the patients who received drugs alone has a 25% increase. However, HDL2-C, an HDL component thought to account for much of HDL's cardioprotective benefit, rose by 42% with drugs alone but was unchanged in patients who also received antioxidants [17].. Although the study was small and has not been replicated, it casts further doubt on the value of antioxidant supplementation [18].

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