

## Antioxidant Vitamins, Cancer, and Cardiovascular Disease

In 1850, an article on the origin of epidemic yellow fever and malaria appeared in the *Boston Medical and Surgical Journal*.<sup>1</sup> The anonymous author referred to earlier reports that "those who slept under musquito [sic] netting escaped the disease" and that "a gauze screen in a window adds much to the security of . . . the occupant of a chamber, in even the most unsound places." These observations, which now seem prescient, were used to support the theory that epidemics result from infective spores carried by the wind from decaying organic matter; the netting and screens were believed to provide a mechanical barrier to these particles. The true reason screens are protective was not identified until the studies of malaria by Ronald Ross in 1898 and of yellow fever by Walter Reed in 1902.

More recently, scores of epidemiologic studies have noted a lower risk of cancer and cardiovascular disease among persons whose diets include a relatively large amount of vegetables and fruits.<sup>2</sup> A popular explanation, both within the scientific community and among members of the public, is that antioxidant vitamins in vegetables and fruits prevent carcinogenesis and atherogenesis by interfering passively with oxidative damage to DNA and lipoproteins.<sup>3,4</sup> Beta carotene has received particular attention as a disease-preventing antioxidant, with numerous favorable reports in scientific journals, and sales of supplements have soared. Although two small clinical trials found no protective effect of beta carotene<sup>5,6</sup> and one large trial from Finland even suggested that it increased mortality from lung cancer and cardiovascular disease,<sup>7</sup> there has been a persistent expectation that larger trials and longer periods of follow-up would ultimately demonstrate the benefits of beta carotene.

Two reports in this issue of the *Journal* should put to rest any remaining hopes that, for adults, beta carotene supplements may be an effective means of lowering the risk of cancer and cardiovascular disease. The Physicians' Health Study followed more than 22,000 U.S. male doctors treated with 50 mg of beta carotene or placebo every other day, for an average of 12 years.<sup>8</sup> The trial was conducted in an exemplary manner in virtually every respect, and its results unequivocally rule out the possibility that there is even a slight reduction in the incidence of cancer or mortality from cardiovascular disease with such supplementation. The Beta-Carotene and Retinol Efficacy Trial (CARET) studied more than 18,000 persons at elevated risk for lung cancer because of exposure to asbestos or cigarette smoking. They were treated daily with beta carotene (30 mg) and retinyl palmitate (25,000 IU), or with placebo, for an average of four years.<sup>9</sup> The trial was ended early when the researchers recognized an elevated risk of death from lung cancer in the group receiving the supplements.

The lack of efficacy of beta carotene in preventing cancer contrasts starkly with the promising findings of numerous studies of retinoids in the prevention, or even the treatment, of cancer.<sup>10</sup> Retinoids are a family of chemical substances related to retinol (vitamin A). They include retinol and its esters (the common forms in which retinoids are ingested as supplements or in food); all-*trans*-, 9-*cis*-, and 13-*cis*-retinoic acids; and synthetic analogues of these substances. Each has a characteristic pattern of metabolism, pharmacokinetics, and interaction with cellular receptors. All-*trans*- and 9-*cis*-retinoic acids, but not retinol, serve as ligands for the six nuclear retinoid-receptor proteins (transcription factors) that mediate the effects of retinoids by regulating gene expression.<sup>11</sup>

The powerful biologic activity of individual retinoids, exactly like that of steroid hormones, resides in these specific receptor interactions. There is no known nuclear receptor for beta carotene, and beta carotene is poorly converted to retinol, whose metabolism to the active retinoic acids is itself tightly regulated. Thus, mechanistic data do not predict a profound effect of beta carotene in the prevention of cancer. Nor do they explain why beta carotene would increase the incidence of cancer, even among smokers, as was found in both the CARET study and the trial from Finland (although not in the Physicians' Health Study).

The disappointing results of the clinical trials of beta carotene reaffirm the importance of solid scientific knowledge as the basis of disease-prevention strategies. Inferences that beta carotene can prevent cancer and cardiovascular disease were drawn largely from observations of a lower risk associated with vegetable and fruit consumption; they lacked strong support from clinical trials or mechanistic studies. Although studies in animals suggested that beta carotene might prevent damage to DNA and perhaps retard the initiation of carcinogenesis, there was little evidence that it suppresses the progression of neoplasia after exposure to carcinogens. There also was no clear evidence that beta carotene inhibits the oxidation of low-density lipoproteins, the principal proposed mechanism of its postulated antiatherogenic properties.

The most effective preventive agents are likely to be those that retard the progression of disease — by normalizing aberrant gene function in early neoplasia, for example. An understanding of processes such as these should guide our choice of agents for testing in human trials, and in this regard — and with hindsight — beta carotene has not emerged as a strong candidate. Nevertheless, the two clinical trials reported in this issue of the *Journal* ought to be seen as representing a triumph of the scientific process rather than a failure of therapy. Their results send a clear message to the public, and the tens of millions of dollars spent annually on beta carotene supplements should now be diverted to more useful purposes.

A third paper in this issue of the *Journal* offers another intriguing observation without a clear explanation. Kushi and his colleagues note that in a group of more than 34,000 postmenopausal women, mortality from coronary heart disease was lower among those whose initial dietary reports indicated a relatively high intake of vitamin E from food.<sup>12</sup> The consumption of vitamin E supplements by these women was not associated with a decrease in risk, and prior epidemiologic studies have been inconsistent on this point. Data from clinical trials are also inconsistent. The trial from Finland found no effect on mortality from cardiovascular disease among those receiving 50 mg of vitamin E daily,<sup>7</sup> but another trial has suggested a reduction in the incidence of nonfatal myocardial infarction with larger doses of supplements.<sup>13</sup> Thus, the study by Kushi et al., like the many previous epidemiologic studies of vitamin E, beta carotene, and other antioxidants, gives no clear guidance to the public about the value of antioxidant-vitamin supplements.

On the other hand, no one should discount the importance of the findings of epidemiologic studies of diet and chronic disease. In most such studies, persons who ate a relatively large quantity of vegetables, fruits, and grains were found to have a profoundly lower risk of death, particularly from cardiovascular disease and cancer. Antioxidant vitamins may not account for all (or even any) of the benefits associated with this dietary pattern, and the myriad other substances in plants should be examined for possible preventive properties. We need sound scientific studies both to identify the true mechanisms underlying the epidemiologic observations and to validate their importance in clinical trials. For now, while we await a better understanding of these mechanisms, consumption of more vegetables and fruits, like the use of mosquito nets and window screens, seems a prudent preventive strategy.

E. Robert Greenberg, M.D.  
Michael B. Sporn, M.D.  
*Dartmouth Medical School*  
*Lebanon, NH 03756*

## References

1. Parallel passages on the fungous theory of epidemics. *Boston Med Surg J* 1850;41:138-40.
2. National Research Council, Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences. *Diet and Health: Implications for reducing chronic disease risk*. Washington, D.C.: National Academy Press, 1989.
3. Byers T, Perry G. Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers. *Annu Rev Nutr* 1992;12:139-159. [[CrossRef](#)][[Medline](#)]
4. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease: a critical review of epidemiologic and clinical trial data. *Ann Intern Med* 1995;123:860-872. [[Abstract/Full Text](#)]
5. Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. *N Engl J Med* 1990;323:789-795. [[Abstract](#)]
6. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 1994;331:141-147. [[Abstract/Full Text](#)]
7. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029-1035. [[Abstract/Full Text](#)]
8. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145-1149. [[Abstract/Full Text](#)]
9. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150-1155. [[Abstract/Full Text](#)]
10. Hong WK, Itri LM. Retinoids and human cancer. In: Sporn MB, Roberts AB, Goodman DS, eds. *The retinoids: biology, chemistry, and medicine*. 2nd ed. New York: Raven Press, 1994:597-630.
11. Mangelsdorf DJ, Umesono K, Evans RM. The retinoid receptors. In: Sporn MB, Roberts AB, Goodman DS, eds. *The retinoids: biology, chemistry, and medicine*. New York: Raven Press, 1994:319-49.
12. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med* 1996;334:1156-1162. [[Abstract/Full Text](#)]
13. Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996;374:781-786. [[CrossRef](#)]