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Editorial

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Beta carotene and cancer: risk or protection?

Beta carotene, vitamin A, and its synthetic and naturally occurring analogues, the retinoids, have attracted wide interest as possible chemopreventive agents against lung cancer (1—3). Some 20 years ago, they were identified as potential chemopreventive agents in lung from epidemiologic data showing an inverse correlation between vitamin A blood levels and lung cancer (4). Beta carotene (a precursor of vitamin A) is found in deep yellow, orange, or dark green fruits and vegetables such as carrots, peaches, apricots, spinach, and broccoli. It is an antioxidant which may protect the critical cellular macromolecules from oxidative damage. In human "biomarker" studies, retinoids have reversed preneoplastic bronchial lesions induced by cigarette smoking (5) and reduced the incidence of micronuclei in buccal smear cells (6) and in sputum cells (7); however, no reduction in sputum atypia was found in a randomized intervention trial with former asbestos workers (8).

Strong evidence exists that diets high in fruit and vegetables are protective against cancer, lung cancer in particular (9). The results of epidemiologic studies consistently show that high intake of fruits and vegetables that are rich in carotenoids has been associated with a decreased risk of cancer at a number of common sites (7, 9). The association is the most consistent for lung cancer and stomach cancer, and the least consistent for breast, prostate, esophageal, and oral cancer. The results of prospective studies show a remarkable consistency for the association of increased lung cancer risk with either an infrequent consumption of dark green and yellow fruits and vegetables, low levels of dietary carotenoids, or low plasma beta carotene levels.

Primary prevention of cancer refers to the elimination or avoidance of exposure to carcinogens. It is the first and, in many instances, the most important and only practical form of prevention (10). However, during the last decade there has been increasing interest in "chemoprevention" (ie, using specific natural or synthetic chemicals to reverse, suppress, or prevent the process of carcinogenesis) (4, 11). A particular aspect of chemoprevention is the "intervention trial." Such trials provide means of testing hypotheses concerning (cancer) prevention (12).

In the last decennium, several intervention trials were initiated to see if the supplementation of vitamins or micronutrients for subjects at high risk of cancer could be effective in decreasing the risk. Such studies have been done among smokers (ATBC study) and highly asbestos-exposed workers (CARET study) and in groups with a high risk of developing epithelial tumors of the respiratory tract. In these studies, beta carotene has been particularly popular as a chemopreventive agent.

Investigators conducting the Beta Carotene and Retinol Efficacy Trial (CARET) in the United States, a large study of the combination of beta carotene and vitamin A as preventive agents for lung cancer among high-risk men and women, terminated the intervention in January 1996 after an average of four years of treatment and told the 18 314 participants to stop taking their vitamins. Interim study results had indicated that the supplements provided no benefit and may be causing harm.

The CARET study was carried out in six areas of the United States. The study was comprised of both current (60%) and former (39%) heavy smokers, including asbestos-exposed smokers (22%). One-half of the CARET participants took a combination of beta carotene and vitamin A, and the other half took inactive placebos. The dose of beta carotene in CARET was 30 mg · d^{-1} (which is equivalent to 50 000 IU of vitamin A or about five medium-sized carrots). Vitamin A was given as retinyl palmitate in a dose of 25000 IU (13).

The CARET results showed 28% more lung cancers and 17% more deaths among the participants taking beta carotene and vitamin A. These interim results were similar to those published earlier from the Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Trial carried out in Finland (14). In the ATBC study, more than 29 000 middle-aged male smokers were randomly assigned to 50 mg of alpha tocopherol, 20 mg of beta carotene, both, or a placebo daily for five to eight years. With regard to lung cancer, which was the primary specified end point, the trial failed to detect any significant protective effect of either of the vitamins. In fact, the study showed 18% more lung cancers and 8% more deaths at the time of the termination of the intervention in the group of smokers treated with 20 mg of beta carotene daily. However, when the placebo group was divided according to quartiles with regard to serum beta carotene concentration, the incidence of lung cancer was higher among the subjects in the lowest quartile group rather than among those in the highest.

A third large intervention trial, carried out among 28 000 male physicians in the United States, ended on schedule, at the end of 1995. This study, in which half of the physicians took carotene supplements and half took placebos for 12 years, has shown no significant evidence of benefit or harm on cancer or cardiovascular disease between the beta carotene (50 mg every other day) and placebo groups in its primarily nonsmoker (89%) population (15).

The daily dose of beta carotene used in the ATBC study (20 mg) increased the serum concentrations of beta carotene more than 10-fold. The dose in the CARET study was even higher. In the ATBC study, between one-quarter and one-third of the participants reported yellowing of the skin. The dose in the two major intervention studies has, therefore, been about as high as it can be.

In spite of the strong association of vitamin A and beta carotene with a reduced incidence of cancer in epidemiologic studies, it has not been proved that these vitamins themselves are protective. The results of the large-scale intervention trials on the potential benefits of beta carotene supplementation do not provide any support of the protective effects, and, in fact, they raise serious questions about the safety of beta carotene supplements for the general public.

There may be issues of dose and timing. However, the serum concentrations after supplementation were not considered to be at "toxic" levels. The timing of intervention is more problematic. Beta carotene is possibly more effective in earlier stages of lung carcinogenesis than in later stages. This is, however, only speculation. After obtaining the evidence from the large intervention trials, the assumption that beta carotene is not protective but causative, especially among current cigarette smokers, must be considered. Pharmacological doses of supplemental beta carotene do not appear to be beneficial in the prevention of cancer, and the trials seem to provide evidence for detriment in smokers. Pharmacological beta carotene supplementation should therefore be discouraged. Avoidance of exposure to carcinogens remains the first and most important form of prevention.

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