The Effect of Long-Term β-Carotene and Vitamin A Administration on Serum Concentrations of α-Tocopherol[1]

Gary E. Goodman,[2] Barbara J. Metch, and Gilbert S. Omenn

Fred Hutchinson Cancer Research Center, Seattle, Washington 98104 [G. E. G., B. J. M., G. S. O.], School of Public Health, University of Washington, Seattle, Washington 98195 [G. E. G., G. S. O.], and Swedish Medical Center Tumor Institute, Seattle, Washington 98104-2092 [G. E. G.]

Abstract

Many micronutrients are currently being tested for cancer prevention activity. A short-term study recently suggested that two of these nutrients, β-carotene and α-tocopherol, may have an adverse interaction, with β-carotene supplementation leading to markedly decreased serum concentrations of α-tocopherol. We have analyzed the effect of β-carotene supplementation on serum concentrations of α-tocopherol in 2319 participants enrolled in the Carotene and Retinol Efficacy Trial who have taken β-carotene and vitamin A for up to 6 years. One thousand thirty-five participants enrolled in two pilot trials to the Carotene and Retinol Efficacy Trial had serum collected at yearly intervals; an additional 1284 recently recruited participants had serum collected at biennial intervals. Using standard high pressure liquid chromatography techniques, with attention to quality control, these samples were analyzed for β-carotene and α-tocopherol. After up to 6 years of supplementation with β-carotene (30 mg/day) and vitamin A (25,000 international units/day) we found a small but statistically significant increase in the serum concentration of α-tocopherol in participants taking the active agents. No evidence of a decrease was found in any of the subpopulations examined. We conclude that long-term supplementation with the combination of β-carotene and vitamin A does not decrease serum concentrations of α-tocopherol. Our long-term trial validates results from several shorter trials conducted by others. The concept of adverse interactions between supplemental micronutrients is important. All cancer prevention trials should closely monitor serum concentrations of micronutrients, as well as the incidence of other significant disease.

Introduction

Retinol, β-carotene, and α-tocopherol currently are being investigated as potential cancer prevention agents (1–3). Although all three have been available for many years as over-the-counter supplements, there have been few studies evaluating their long-term toxicity and potential interactions with each other or with other micronutrients.

In a short-term Phase I toxicity trial of supplemental β-carotene in normal volunteers, Xu *et al.* (4) recently reported a progressive decrease in the serum concentration of α-tocopherol during 9 months of daily supplementation with 15, 30, 45, or 60 mg of β-carotene (4). Since reports suggest that the incidence of both cancer and coronary artery disease is inversely related to serum α-tocopherol concentrations (5, 6), this finding raised a concern that widespread use of β-carotene as a dietary supplement or a food additive could be detrimental to public health.

As part of CARET,[3] which is testing the effect of β-carotene and retinyl palmitate supplementation on the incidence of lung cancer in high-risk populations, we have been carefully monitoring potential side effects of these agents, including their effect on micronutrient status (3). We report here the effect of long-term β-carotene supplementation on α-tocopherol serum concentrations in the CARET study population.

Materials and Methods

In 1985, we initiated CARET with pilot trials of β-carotene and retinol in 1029 smokers and 816 asbestos-exposed workers at risk for lung cancer (7, 8). The smokers were randomized to: (*a*) placebo; (*b*) β-carotene, 30 mg/day; (*c*) retinol, 25,000 IU/day; or (*d*) β-carotene, 30 mg plus retinol, 25,000 IU/day. Asbestos-exposed workers were randomized to (*a*) placebo or (*b*) β-carotene, 15 mg plus retinol, 25,000 IU/day.

At the conclusion of the pilot trials, we found that the agents appeared to be safe as either single supplements or in combination (7, 8). Recruitment of an additional 16,000 participants in 6 geographic sites occurred between January 1989 and July 1994. This expanded trial, designated CARET, is a two-arm placebo-controlled trial testing whether the daily administration of β-carotene (30 mg) plus retinyl palmitate (25,000 IU) can decrease the incidence of lung cancer in these high-risk populations (16).

With the additional recruitment, all pilot participants who were receiving any active vitamins had their dosage and treatment changed, where necessary, to match the combination used in CARET; pilot participants randomized to placebos continued to receive placebos. These changes did not result in unblinding since the study capsules were changed for all participants to new capsule formulations. Participants recruited and randomized after the pilot phase

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[1] Supported by National Cancer Institute Grant CA34837.
[2] To whom requests for reprints should be addressed, at Fred Hutchinson Cancer Research Center, CARET Coordination Center, MP-859, 1124 Columbia Street, Seattle, WA 98104-2092.

[3] The abbreviations used are: CARET, Carotene and Retinol Efficacy Trial; NIST, National Institute of Standards and Technology; IU, international unit.

otene (20 mg/day) and at 2 months found no change in α-tocopherol serum concentration (12). In addition, Nierenberg *et al.* (13) recently reported no change in serum α-tocopherol concentrations after 9 months in 241 participants randomized in the Polyp Prevention Study to either oral β-carotene (25 mg/day) or placebo.

We cannot explain the differences between our findings and those projected by Xu *et al.* (4). The intervention in the Arizona trial consisted of single agent β-carotene in doses of 15–60 mg. Our participants, as well as those enrolled in the McLarty trial, received a combination of β-carotene and retinyl palmitate. It is possible that the coadministration of 25,000 IU of retinyl palmitate with β-carotene protects against a fall in the serum concentration of α-tocopherol. However, the short-term studies of Willett *et al.* (11), Albanes *et al.* (12), and Nierenberg *et al.* (13) also found no change in α-tocopherol concentrations after the administration of β-carotene alone.

The baseline mean concentrations of α-tocopherol in the population studied by Xu *et al.* (4) were 7.76–8.44 μg/dl (4). These values are lower than our efficacy cohort with a baseline mean of 15.0 μg/dl (median, 13.2 μg/dl) and lower than populations studied by McLarty (10), Albanes *et al.* (12), Nierenberg *et al.* (13), Sinha *et al.* (14), and Brown *et al.* (15), who found mean α-tocopherol serum concentrations of 13.2 μg/ml, 13.2 μg/ml, 12.7 μg/ml, 10.2 μg/ml, and 9.8 μg/ml, respectively. It is unclear why these reports of α-tocopherol serum concentrations vary widely among populations. Most laboratories, including ours and the Arizona group (4), participate in the NIST quality control assessment for β-carotene and α-tocopherol, so that differences in analytic method are unlikely to explain the variance. It is possible that the lower serum concentrations of α-tocopherol in the Arizona population may have made them respond differently to β-carotene supplementation than other populations with higher values. However, we saw no evidence of such a trend within our efficacy cohort. Participants in the lowest quartile of α-tocopherol concentrations at baseline (<10.7 μg/ml) showed a slight increase in concentrations at 2 years (active arm mean change, +2.8 μg/ml; placebo mean change, +2.9 μg/ml), while those in the upper quartile (>16.8 μg/ml) showed a slight decrease (active mean change, −1.7 μg/ml; placebo, −3.7 μg/ml).

The mean ages of our cohorts (57–59 years) were similar to those of the Arizona group (57–58 years). Sex is also unlikely to account for the differences in our findings since the Arizona group had a higher percentage of women. Dietary differences between populations living in different regions of the United States (especially the Pacific Northwest and the desert Southwest), as well as differences in health status, could be part of the explanation. The Arizona population consisted of nonsmokers, whereas our trial and those of McLarty (10) and Albanes *et al.* (12) consisted of smokers and former smokers (we found no differences in the baseline serum concentrations of α-tocopherol between our efficacy current smokers and former smokers). It is not known if never-smokers have lower serum concentrations of α-tocopherol. Although we do not have baseline α-tocopherol values on our pilot asbestos-exposed population (16% never smokers), in the follow-up samples of this group we observed no consistent differences in α-tocopherol concentrations between current, former, and never-smokers. Hence, it is unlikely that smoking status explains the differences in baseline α-tocopherol values.

Many micronutrients are being tested as chemoprevention agents. The potential for adverse interactions is an important topic since other disease processes may be affected adversely. Careful monitoring in our long-term trial as well as shorter trials by others has shown that long-term β-carotene supplementation does not adversely affect the serum concentrations of α-tocopherol. In ongoing and planned cancer chemoprevention trials, it will be important to measure the serum concentration of known micronutrients and to monitor the incidence of other medical diagnoses such as cardiovascular disease and cataracts, both of which may be affected by micronutrient status.

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