

1: N Engl J Med. 1994 Apr 14;330(15):1029-35.

**The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group.**

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**BACKGROUND.** Epidemiologic evidence indicates that diets high in carotenoid-rich fruits and vegetables, as well as high serum levels of vitamin E (alpha-tocopherol) and beta carotene, are associated with a reduced risk of lung cancer. **METHODS.** We performed a randomized, double-blind, placebo-controlled primary-prevention trial to determine whether daily supplementation with alpha-tocopherol, beta carotene, or both would reduce the incidence of lung cancer and other cancers. A total of 29,133 male smokers 50 to 69 years of age from southwestern Finland were randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo. Follow-up continued for five to eight years. **RESULTS.** Among the 876 new cases of lung cancer diagnosed during the trial, no reduction in incidence was observed among the men who received alpha-tocopherol (change in incidence as compared with those who did not, -2 percent; 95 percent confidence interval, -14 to 12 percent). Unexpectedly, we observed a higher incidence of lung cancer among the men who received beta carotene than among those who did not (change in incidence, 18 percent; 95 percent confidence interval, 3 to 36 percent). We found no evidence of an interaction between alpha-tocopherol and beta carotene with respect to the incidence of lung cancer. Fewer cases of prostate cancer were diagnosed among those who received alpha-tocopherol than among those who did not. Beta carotene had little or no effect on the incidence of cancer other than lung cancer. Alpha-tocopherol had no apparent effect on total mortality, although more deaths from hemorrhagic stroke were observed among the men who received this supplement than among those who did not. Total mortality was 8 percent higher (95 percent confidence interval, 1 to 16 percent) among the participants who received beta carotene than among those who did not, primarily because there were more deaths from lung cancer and ischemic heart disease. **CONCLUSIONS.** We found no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta carotene. In fact, this trial raises the possibility that these supplements may actually have harmful as well as beneficial effects.

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1: J Natl Cancer Inst. 1996 Nov 6;88(21):1550-9.

## **Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial.**

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**BACKGROUND:** Evidence has accumulated from observational studies that people eating more fruits and vegetables, which are rich in beta-carotene (a violet to yellow plant pigment that acts as an antioxidant and can be converted to vitamin A by enzymes in the intestinal wall and liver) and retinol (an alcohol chemical form of vitamin A), and people having higher serum beta-carotene concentrations had lower rates of lung cancer. The Beta-Carotene and Retinol Efficacy Trial (CARET) tested the combination of 30 mg beta-carotene and 25,000 IU retinyl palmitate (vitamin A) taken daily against placebo in 18314 men and women at high risk of developing lung cancer. The CARET intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harm; there were 28% more lung cancers and 17% more deaths in the active intervention group (active = the daily combination of 30 mg beta-carotene and 25,000 IU retinyl palmitate). Promptly after the January 18, 1996, announcement that the CARET active intervention had been stopped, we published preliminary findings from CARET regarding cancer, heart disease, and total mortality. **PURPOSE:** We present for the first time results based on the pre-specified analytic method, details about risk factors for lung cancer, and analyses of subgroups and of factors that possibly influence response to the intervention. **METHODS:** CARET was a randomized, double-blinded, placebo-controlled chemoprevention trial, initiated with a pilot phase and then expanded 10-fold at six study centers. Cigarette smoking history and status and alcohol intake were assessed through participant self-report. Serum was collected from the participants at base line and periodically after randomization and was analyzed for beta-carotene concentration. An Endpoints Review Committee evaluated endpoint reports, including pathologic review of tissue specimens. The primary analysis is a stratified logrank test for intervention arm differences in lung cancer incidence, with weighting linearly to hypothesized full effect at 24 months after randomization. Relative risks (RRs) were estimated by use of Cox regression models; tests were performed for quantitative and qualitative interactions between the intervention and smoking status or alcohol intake. O'Brien-Fleming boundaries were used for stopping criteria at interim analyses. Statistical significance was set at the .05 alpha value, and all P values were derived from two-sided statistical tests. **RESULTS:** According to CARET's pre-specified analysis, there was an RR of 1.36 (95% confidence interval [CI] = 1.07-1.73; P = .01) for weighted lung cancer incidence for the active intervention group compared with the placebo group, and RR = 1.59 (95% CI = 1.13-2.23; P = .01) for weighted lung cancer mortality. All

subgroups, except former smokers, had a point estimate of RR of 1.10 or greater for lung cancer. There are suggestions of associations of the excess lung cancer incidence with the highest quartile of alcohol intake (RR = 1.99; 95% CI = 1.28-3.09; test for heterogeneity of RR among quartiles of alcohol intake has  $P = .01$ , unadjusted for multiple comparisons) and with large-cell histology (RR = 1.89; 95% CI = 1.09-3.26; test for heterogeneity among histologic categories has  $P = .35$ ), but not with base-line serum beta-carotene concentrations. CONCLUSIONS: CARET participants receiving the combination of beta-carotene and vitamin A had no chemopreventive benefit and had excess lung cancer incidence and mortality. The results are highly consistent with those found for beta-carotene in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study in 29133 male smokers in Finland.

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