

## Beta-carotene did not work: aftermath of the ATBC study

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### Abstract

The results of the ATBC study, the first large intervention trial of antioxidants, were intriguing. While the possibility that  $\beta$ -carotene may in some circumstances enhance carcinogenesis has now been confirmed in another large trial, the mechanisms of action remain obscure. © 1997 Elsevier Science Ireland Ltd.

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### 1. Introduction

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) was a double-blind trial testing the efficacy of  $\alpha$ -tocopherol and  $\beta$ -carotene supplementation in prevention of lung cancer in particular and cancer in general. In all, 29 133 male smokers 50–69 years of age were randomly assigned to receive *dl*- $\alpha$ -tocopherol (50 mg),  $\beta$ -carotene (20 mg), both, or placebo daily for 5–8 years (median 6.1 years). The 2 × 2 factorial design allows analyses of the end-points in combinations of the original treatment groups:  $\alpha$ -tocopherol (AT) vs. no AT and  $\beta$ -carotene (BC) vs. no BC [1].

AT had no effect on the incidence of lung cancer. The incidence (per 10 000 person-years) among those receiving AT was 53.2 and among those not receiving AT, 54.5. Against expectations, the men who received BC presented with a higher incidence (+16%) of lung cancer than those who did not get BC (incidence of

cases 58.0 vs. 49.7). There were 204 cases in the original AT group, 242 in the BC group, 240 in the AT + BC group, and 208 in the placebo group [2,3].

The results do not support the hypothesis that supplementation with alpha-tocopherol or beta-carotene could protect against lung cancer. In fact, this trial was the first to advocate the possibility that beta-carotene may also be harmful. Since the end of the ATBC Study, two other large intervention trials using beta-carotene have been reported. The Beta-Carotene and Retinol Efficacy Trial (CARET) reported a 28% increase of lung cancer in the supplemented group [4] and the Physicians' Health Study reported a lack of any effect by supplemental beta-carotene in the primarily non-smoking population [5]. Several possible explanations for our results and those from subsequent trials have been offered.

(1) Wrong timing of intervention. The median follow-up of 6 years may have been too short for AT to show an effect on the decade-long carcinogenesis. The post-trial follow-up is intended to resolve this issue. The appropriate timing of an intervention relates also to the period in the carcinogenic process

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during which the active substances are presumed to be effective. Prior evidence implied that beta-carotene may affect the process at later rather than early phase and thus older smokers were considered a valid target group for the intervention. The true mechanism of action of BC is still obscure.

(2) Wrong target group. Smoking is one of the few easily identified, population level risk factors for cancer. It takes decades for cancer to become clinically detectable and thus its incidence starts to increase only after 50 years of age. Practical considerations made it impossible to increase the follow-up time by including younger smokers who might have benefitted from the effects of AT and BC. On the other hand, the harmful effect of BC seem be related to smoking and limited to smokers.

(3) Wrong dose. Most of the evidence of the useful effects of AT and BC is related to dietary intake. The doses used clearly exceeded these levels. Higher levels of BC would also have endangered the blindness of the study (i.e. from carotenodermia).

(4) Wrong substance. It is possible that BC is not the potent component in fruits and vegetables, but only a marker of some other factor(s).

(5) Pro-oxidant effect. There is limited evidence that BC could function as a pro-oxidant at higher concentrations. The vitamin C reserves required for the regeneration of alpha-tocopheroxyl radical might not have been sufficient.

(6) Tipping the balance. The health of an organism depends on the carefully kept balance between free radicals and antioxidants. Giving antioxidants abundantly may have disturbed homeostatic and physiologic processes.

Considering the length of carcinogenesis from the first genotoxic event to the appearance of clinically detectable tumor and the swiftness with which the beta-carotene effect appeared (after about 2 years of

supplementation), it is obvious that the observed effect is related to the growth of cells that have already undergone malignant transformation. Thus, it has been suggested that beta-carotene could favor, through an as yet unexplained mechanism, the growth of initiated cells.

It is clear that we need more information to resolve the role of antioxidants in carcinogenesis.

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