β-Carotene and Lung Cancer Promotion in Heavy Smokers—a Plausible Relationship?

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Initial findings from two major clinical trials, the Beta-Carotene and Retinol Efficacy Trial (CARET) in the United States (1) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) in Finland (2), unexpectedly showed that supplemental β-carotene alone or in combination with retinol appeared to increase the risk of lung cancer, particularly in current smokers. CARET also reported that the combination of retinol and β-carotene increased the risk of lung cancer in asbestos workers, most of whom were current or former smokers. In contrast, the U.S. Physicians' Health Study (3) reported that supplemental β-carotene did not increase the risk of lung or other cancers, even in smokers. Finally, a consistent body of epidemiologic data (4) shows that increased consumption of β-carotene-rich foods and higher blood levels of β-carotene are associated with a reduced risk of lung cancer.

No plausible explanation has been offered for why β-carotene increased the risk of lung cancers in the ATBC Study (2) and in CARET (1) but did not increase the risk of lung cancer in the Physicians’ Health Study (3) and failed to increase the risk of cancers at other organ sites in these and other trials (2,3,5). Also unresolved is why β-carotene should increase the risk of lung cancer in current but not former smokers (1).

In this issue of the Journal, ATBC Study investigators (6) and CARET investigators (7) present additional analyses from these important trials. Subgroup analyses by Albanes et al. (6) indicate that the adverse effects of supplemental β-carotene in the ATBC Study are restricted to persons who smoked one pack of cigarettes or more per day or who drank above-average levels of alcohol. The new finding that lung cancer risk was not elevated by supplemental β-carotene in moderate intensity smokers in the ATBC Study extends the related finding from CARET that former smokers who received the supplements were not at increased risk. CARET investigators similarly examined their data for evidence of an alcohol effect; results suggested an interaction with alcohol (7), although the lack of a dose–response effect reduces confidence that this interaction is real. Other intriguing findings emerge, such as the finding in both trials that large-cell cancers were increased to a greater degree following β-carotene supplementation than other histologic types (6,7).

Given the new and older findings from these and other β-carotene trials, what can be surmised about mechanisms of action, causality, and generalizability?

The aggregate data suggest that concurrent cigarette smoke exposure (1,7) of relatively high intensity (6) is necessary for a promotional effect of supplemental β-carotene on lung cancer to occur. This hypothesis is consistent with a direct interaction between cigarette smoke and β-carotene. The gas phase of cigarette smoke is highly oxidative, possessing an array of free radicals (8,9). Handelman et al. (10) exposed human plasma to the gas phase of cigarette smoke to assess effects on carotenoids, tocopherols, and retinol. Exposure of plasma to room air did not degrade these micronutrients. In contrast, exposure of plasma to cigarette smoke led to the destruction of carotenoids and α-tocopherol in the plasma, despite their physical location in lipoproteins and presumed protection by endogenous antioxidants. Oxidation of other plasma lipids was minimal, suggesting selective oxidative susceptibility of carotenoids and α-tocopherol.

Thus, it is reasonable to propose that β-carotene in the lungs of heavy smokers undergoes oxidative attack. While researchers have not yet identified oxidation products of β-carotene induced by tobacco smoke, products of β-carotene induced by other oxidants have been characterized (11-13). The chemical structures of many of these products (i.e., epoxides) suggest that they would be unstable under conditions of oxidative stress, further contributing to oxidation. This hypothesis is consistent with observations in vitro that β-carotene can have pro-oxidant activity, particularly under conditions of ambient (14) or higher (15,16) oxygen tensions. Conditions in the lungs of heavy smokers may tip the β-carotene antioxidant–pro-oxidant balance toward a pro-oxidant state. Agents that induce a cellular pro-oxidant state are known to act as tumor promoters (17).

Auto-oxidation of β-carotene in vitro is dose dependent (15,16). This dose dependence may explain why lung cancer risk was not elevated among β-carotene-supplemented smokers in the Physicians’ Health Study—blood levels of β-carotene in this study (1.2 μg/mL) were considerably lower than those achieved in subjects receiving the supplements in the ATBC Study and in CARET (median = 3.0 and 2.1 μg/mL, respectively) (1-3). As detailed by Albanes et al. (6) in this issue of the Journal, participants with the highest blood β-carotene levels following supplementation in the ATBC Study were not at greater risk than participants with lower levels. These lower
levels (<2.3 μg/mL), however, were in excess of average levels achieved in the Physicians’ Health Study and well beyond levels (0.05-0.5 μg/mL; 5th-95th percentile) in the U.S. population (18).

How does an oxidative mechanism explain the CARET findings of enhancement of lung carcinogenesis in asbestos workers, only 38% of whom were current smokers (1)? Asbestos fibers contain iron, a powerful catalyst for oxidation (19). Moreover, inflammatory cells recovered by bronchoalveolar lavage from nonsmokers with asbestosis spontaneously release significantly increased amounts of superoxide anion and hydrogen peroxide relative to those from normal individuals (20). Thus, in theory, the inflammatory process in the asbestos-exposed lung sets the stage for the formation of harmful carotenoid oxidation products. To test this hypothesis, a comparison of the effects of the β-carotene intervention in those participants with asbestos versus those with asbestos exposure but without the clinical manifestations might be revealing.

A potential adverse role for retinol in this process should not be overlooked. In CARET, where supplemental retinol was combined with β-carotene, the relative risk in male current smokers, excluding the asbestos-exposed, was 1.39 (7), compared with a relative risk of 1.16 in the ATBC Study (6). This excess risk in CARET occurred despite a shorter median duration of supplementation than in the ATBC Study (3.7 years versus 6.1 years) and despite lower median plasma β-carotene levels in subjects receiving the supplements (2.1 versus 3.0 μg/mL). Retinol can be a pro-oxidant in vitro, has enhanced carcinogenesis in animal studies, and increases risk of several cancers in epidemiologic studies (21). An adverse interaction between retinol and ethanol in human cancer had been postulated previously (21).

Participants with higher serum β-carotene concentrations at entry into CARET (7) and the ATBC Study (6) had fewer subsequent lung cancers, even among those who received the supplements. How does one explain this result? Base-line serum concentrations of β-carotene reflect fruit and vegetable intake; fruits and vegetables contain many antioxidant substances (22), some of which may serve as traps to protect β-carotene from oxidation by tobacco smoke. Fruits and vegetables also contain numerous other compounds with potential cancer-inhibiting properties. These results reaffirm the benefits of consuming foods rich in carotenoids.

The mechanism proposed herein is plausible, and the new findings from both trials that the adverse effect seemed stronger with a longer duration of supplementation add to the weight of the evidence that this finding may be real. It would be useful to determine if β-carotene or its metabolites accelerate the transformation of cells derived from the bronchial epithelium of long-term smokers (23). While the risk of supplemental β-carotene may be real, it seems to be confined to lung cancer in current heavy smokers, possibly heavier drinkers, and those who take high doses of β-carotene. A beneficial effect of β-carotene supplementation in former smokers (1) and micronutrient-deficient populations (24,25) is possible. The ATBC Study data show that subjects in the lowest quartile of serum β-carotene at entry (<0.109 μg/mL) had notably elevated lung cancer rates compared with subjects in the second, third, and fourth quartiles of serum β-carotene at entry, whose lung cancer rates were similar (6). These and other data suggest that the paradigm for nutrient-based cancer chemoprevention may need revision. Interventions aimed at restoring levels of a given nutrient in populations at nutritional risk, preferably via diet change, may be more effective than interventions that emphasize taking populations with adequate nutrient status and supplementing to supra-adequacy. Paracelsus postulated in the 16th century that (a) experimentation is essential in examination of responses to chemicals; (b) one should make a distinction between therapeutic and toxic properties of chemicals; and (c) these properties are sometimes, but not always, indistinguishable by dose (26). The unexpected results of these randomized, prospective trials affirm the wisdom of Paracelsus as it applies to nutrient-based chemoprevention research.

References


