Cigarettes, cancer, and carotenoids: a continuing, unresolved antioxidant paradox$^{1-3}$

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Over the past several decades, evidence has accumulated to support the concept that consumption of diets rich in fruit and vegetables is associated with a lowered risk of cardiovascular disease and various forms of cancer (primarily lung and stomach cancer but also esophageal, oral, breast, and prostate cancer; 1, 2). Such beneficial effects have been associated with the presence of fibers and several antioxidant micronutrients in these food groups, and considerable attention has been given to the carotenoids (primarily β-carotene). This attention was fueled by observed inverse relations between serum β-carotene concentrations and subsequent incidences of cancer (2). It has been claimed that oxidative processes participate in various stages of carcinogenesis (3) and that β-carotene and other micronutrients afford cancer prevention by virtue of their antioxidant properties. Accordingly, increased consumption of fruit and vegetables rich in carotenoids and other antioxidant micronutrients was found to lower urinary indexes of oxidized lipids (malondialdehyde and 8-isoprostane F$_{2\alpha}$) and DNA (8-hydroxy-deoxyguanosine; 8-OhdG) in healthy subjects (4). Although several chemical studies indicated that β-carotene (and other carotenoids) are excellent quenchers of singlet oxygen and that β-carotene may also protect lipids from radical-initiated peroxidation under certain conditions, evidence for similar antioxidant properties of β-carotene in vivo is much less compelling (5). Moreover, the complex multi-stage process of carcinogenesis, in which oxidative processes may play variable and incompletely understood roles, dramatically complicates the general assessment of antioxidant benefit.

The proposed beneficial properties of β-carotene found some support in a few early, small supplementation studies (reviewed in reference 2). For instance, indexes of precancerous lesions in chewers of tobacco and betel quid were reduced with reference to controls (2). For instance, indexes of precancerous lesions in chewers of tobacco and betel quid were reduced with reference to controls (2). The proposed beneficial properties of carotenoids appear to be consistent with findings that cigarette smokers, known to be at increased risk of cardiovascular disease and lung cancer, generally have subnormal serum concentrations of various carotenoids (including β-carotene) and other micronutrients, such as vitamin C. This phenomenon is commonly attributed to the enhanced degradation of carotenoids by the increased oxidative stress associated with smoking and its attendant inflammatory-immune system activation. A major limitation of such an interpretation is the fact that dietary intake of these micronutrients is often lower in smokers than in nonsmokers because smokers generally consume less fruit and vegetables. Associations of adverse health effects with smoking are, however, also observed in passive smokers (3), in whom the contribution of dietary differences might be less obvious but still difficult to rule out.

The study by Alberg et al (6) in this issue of the Journal was performed to further address this issue. These authors carefully investigated the relation between active or passive smoking and serum micronutrient concentrations. By using specimens from the Washington County, MD, serum bank and results from a private census in Washington County, serum micronutrient concentrations of >1500 subjects were assayed in 4 separate laboratories over a 13-y period. Subject groups were divided according to smoking status, distinguishing both current and former active and passive smokers. The study showed that both active smokers and subjects currently living with a smoker had lower serum concentrations of total carotenoids, α-carotene, β-carotene, and cryptoxanthin than did nonsmokers, whereas no significant differences were found for other carotenoids, retinol, or α- and γ-tocopherol. Although the authors were unable to completely rule out differences in dietary factors, the strikingly similar profiles between active and passive smokers with respect to their relative carotenoid deficiencies were suggested to indicate selective (oxidative) depletion of these micronutrients in association with both active and passive smoking.

Of course, the constituents of cigarette smoke are known to be capable of degrading β-carotene and other carotenoids (7, 8), but without measurement of elevated carotenoid oxidation products in smoking subjects it cannot be concluded that smoking causes increased carotenoid metabolism or oxidative degradation. Moreover, the consistent observation of subnormal carotenoid concentrations but unchanged α-tocopherol concentrations (6) suggests that factors other than oxidative stress contribute to the relative carotenoid deficiency seen.

The obvious question arising from the results of Alberg et al is whether correction of such a carotenoid deficit by supplementation...
strategies could minimize the increases in the risks of cancer and heart disease associated with passive smoking. The epidemiologic evidence for such a beneficial role of β-carotene was not supported by several large, randomized supplementation trials. In fact, 2 major trials found increased cancer incidence with β-carotene supplementation in both smokers and asbestos workers, high-risk groups who may already have been in the early stages of cancer development at the start of the study (2). These surprising findings brought up an interesting apparent paradox: how can supplementation with β-carotene (a presumed antioxidant and possible chemopreventive agent) lead to enhanced cancer formation, even though this is thought to involve oxidative processes? Similar paradoxical results were obtained in several other antioxidant (vitamin C or E) intervention studies (9). Although such paradoxical findings are sometimes explained by prooxidant properties of these micronutrients under certain conditions, other properties unrelated to pro- or antioxidant actions should be considered.

In some experimental systems, carotenoids have been found to possess prooxidant properties at high oxygen concentrations, but such actions are considered unlikely under in vivo conditions (3, 8). More consideration has been given to the idea that carotenoid metabolism may be dramatically increased or altered in these high-risk groups, and that certain metabolites or oxidation products of β-carotene could be procarcinogenic, for instance, by interfering with retinoid signaling pathways. Indeed, several recent studies indicated that, although β-carotene itself has anticarcinogenic properties, its oxidized products can facilitate carcinogenesis by promoting DNA damage or by inducing cytochrome P450 enzymes that promote carcinogen activation (2, 10). Such induction of cytochrome P450 enzymes might also enhance the catabolism of retinoic acid, which plays an important role in the control of lung epithelial cell proliferation and differentiation. In a recent study in ferrets, supplementation with β-carotene was found to cause specific down-regulation of the retinoic acid receptor RARβ, which may act as a tumor suppressor gene. Moreover, lung expression of the protooncogenes c-jun and c-fos was found to be elevated in animals that were exposed to cigarette smoke and were also receiving β-carotene supplements (10). Thus, there is now considerable evidence for the formation of carotenoid metabolites or oxidation products with procarcinogenic properties, especially in response to cigarette smoke–induced stress, which may override the proposed antioxidant properties of β-carotene itself. Further identification of the responsible procarcinogenic carotenoid-derived products and their biological activities would help resolve and clarify this issue.

Where do we currently stand? Should carotenoid supplementation still be recommended in subject groups that are at elevated risk of cancer (for example, smokers who have recently quit)? And how strong is our current evidence that β-carotene or other carotenoids can really help prevent cancer in humans? Despite some positive results, most past studies did not show a significant benefit of carotenoid supplementation (2), and epidemiologic studies so far have not confirmed that β-carotene is a principal factor in the reduced risk of disease associated with consumption of fruit and vegetables. Surely, the results of the recent major trials have raised much concern regarding β-carotene supplementation, and we clearly need to better understand the overall bioactive processes involved in carotenoid degradation, especially in high-risk subject groups such as smokers, before such supplementation can be advocated. Further knowledge is also needed regarding the potential biological activities of such carotenoid-related products, or even of high amounts of carotenoids themselves. Given the complex multifactorial etiology of such tobacco-related diseases as lung cancer and atherosclerosis, which involve variable involvement of inflammatory-immune processes and genetic factors that are not easily modulated by such antioxidant micronutrients, the lack of success of supplementation studies with individual micronutrients such as β-carotene does not seem surprising. Recently, indexes of oxidative damage that are presumed to be related to procarcinogenic processes (eg, protein carbonyls, 8-OHdG) were found to be reduced in smokers by supplementation with α-tocopherol but not with β-carotene (11). Linking such findings to cancer epidemiology studies without knowledge of the contribution of oxidative pathways to the various stages of carcinogenesis is certainly difficult. However, such results may further challenge the postulated in vivo antioxidant properties of β-carotene; the proposed anticarcinogenic properties of carotenoids are perhaps unrelated to their presumed antioxidant activities. Although β-carotene is often grouped together with other antioxidant micronutrients, this does injustice to its other biological properties, which include modulation of intercellular communication, immune regulation, growth control, and regulation of metabolic enzymes (2). Finally, an interesting proposal has been put forward that carotenoids may serve as sentinels in the cell, with low β-carotene concentrations indicating the disease stage or progression rather than mediating or causing it (12). In such a case, there would be no rationale for carotenoid supplementation, and other therapeutic or preventive strategies should be sought instead.

In general, the negative outcomes of several supplementation trials and the lack of proof that identifies carotenoids as the primary beneficial components of fruit and vegetables should serve as a warning against unregulated supplementation with these individual micronutrients. Interestingly, the procarcinogenic properties of β-carotene were recently found to be reduced by vitamin E (13), suggesting that, rather than individual micronutrient supplementation, combinations of various micronutrient supplements might be more advantageous. For now, it seems wiser just to stick with the fruit and vegetables themselves, although recent attempts to improve β-carotene synthesis in food groups otherwise deficient in such micronutrients by genetic engineering (14) may add a whole new twist to this discussion.

REFERENCES