Cigarettes: A Smoking Gun in Cancer Chemoprevention

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A growing body of literature indicates that chemopreventive agents may have very different effects in populations that differ by lifestyle or host factors. One such factor of paramount importance is smoking status, which has been shown to predict the effects of micronutrients such as β-carotene or related compounds in smoking-related cancer prevention trials. Some nutrients that appear to reduce the risk of cancer in nonsmokers may actually increase the risk of cancer in smokers, whereas other preventive nutrients may work better in smokers than nonsmokers.

Two landmark trials, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study and Carotene and Retinol Efficacy Trial (CARET), first revealed an important impact of smoking status on chemoprevention. The ATBC trial was a randomized 2 × 2 factorial prevention trial of daily α-tocopherol (1) and/or β-carotene in more than 29,000 male smokers from Finland. Unexpectedly, the men who were randomly assigned to receive supplemental β-carotene had a statistically significantly higher lung cancer risk than did men who did not receive β-carotene. This harmful effect occurred in men who smoked 20 cigarettes or more per day but not in men who smoked less (all ATBC participants were smokers). Therefore, the ATBC suggested that smoking intensity modified the cancer preventive effect of a nutrient. Subsequently, the CARET of β-carotene combined with retinol to prevent lung cancer in men and women smokers and/or asbestos workers found that lung cancer risk was statistically significantly increased among heavy smokers who were smoking at the time of randomization in the active-treatment arm (versus in the placebo arm) (relative risk [RR] = 1.42, 95% confidence interval [CI] = 1.07 to 1.87); heavy smokers who had quit prior to randomization had a statistically nonsignificantly lower lung cancer risk in the treatment arm (versus placebo) (RR = 0.80, 95% CI = 0.48 to 1.31) (2).

Evidence suggesting that tobacco exposure modifies the chemopreventive efficacy of nutrients/nutrient derivatives continues to mount. This evidence comes from observational cohort studies such as that reported by Touvier et al. (3) in this issue of the Journal as well as from clinical trials and animal studies that are summarized later. The Touvier et al. study is one of the first cohort analyses of supplemental β-carotene use and its interaction with tobacco in the risk of tobacco-related cancers in women. The authors reported that ever-smoking women taking supplemental β-carotene were at an increased risk of tobacco-related cancers (RR = 2.14, 95% CI = 1.16 to 3.97) in comparison with ever-smoking women consuming low levels of β-carotene (from foods only). In contrast, never-smoking women taking β-carotene supplements were at a lower risk of tobacco-related cancers (RR = 0.44, 95% CI = 0.18 to 1.07) than were never-smoking women consuming low levels of β-carotene (from foods only). Although quite provocative, these results are subject to certain limitations. Below we discuss some of the limitations in this new study and then discuss the totality of the evidence suggesting that tobacco smoking modifies the chemopreventive efficacy of nutrient supplements.

Despite the impressive size of the Touvier et al. cohort (59,210 noncases and 700 cancer cases), the use of β-carotene supplements was relatively uncommon (2%). When these women were further stratified by smoking and case–control status, the final risk estimates reported above were based on only five never-smoking women and 12 ever-smoking women who took supplements and developed a cancer of interest. Also, the authors used a combined endpoint of “tobacco-related cancers,” which included (in order of highest to lowest incidence) colorectal cancers, thyroid cancers, ovarian cancers, cervical cancers, lung cancers, and other less common cancers. Because not all of these cancers are clearly tobacco related (4), conclusions on the influence of tobacco use are limited. Dose–response conclusions also are problematic. The authors report a statistically significant inverse dose–response relationship for never smokers and a nearly statistically significant positive dose–response relationship for ever smokers. These dose–response findings are limited.
however, by a lack of any dose information for the supplement users in this study, the likely wide range of β-carotene intake in these supplement users, and the difficulty in estimating the true exposure to total β-carotene since β-carotene is much more bioavailable in supplements than in dietary sources (5).

Despite these limitations, the data of Touvier et al. are provocative and help to reinforce the conclusion that future studies of micronutrients and their derivatives should include stratification by smoking status. This conclusion is based on the totality of evidence, which has grown well beyond the results of the ATBC and CARET (6). Randomized controlled trial data on supplemental β-carotene in recurrent colorectal adenomatous polyps (7) and skin cancer prevention (8) show statistically significant or nearly statistically significant interactions of the agent with smoking. Some animal/mechanistic studies also support a biologic interaction between high-dose β-carotene and tobacco exposure (9,10). Another study used plasma carotenoid levels in assessing interactions of these nutrients with tobacco. All the major carotenoids had a statistically significant interaction with tobacco, with higher plasma carotenoid levels being inversely associated with mortality in nonsmokers but also, except for lycopene, being positively associated with mortality in smokers (11). Lycopene was more strongly inversely associated with mortality in nonsmokers (versus other carotenoids), and its lack of a positive association with mortality in smokers is consistent with data from animal models indicating the same lack of interaction (12). In contrast to the carotenoids, there is some evidence that vitamin E is a more effective chemopreventive agent in smokers, at least with regard to prostate cancer (13–15). An ongoing large-scale phase III trial, the Selenium and Vitamin E [prostate] Cancer Prevention Trial (SELECT) (16), will be positioned to address this potential interaction in the future.

Some of the most compelling evidence of a chemopreventive agent—smoking interaction comes from the Lung Intergroup Trial (17), a randomized, placebo-controlled phase III trial of the retinoid 13-cis-retinoic acid (13cRA) in preventing second primary tumors in definitively resected early-stage lung cancer patients. 13cRA was neutral overall but had a statistically significant interaction with smoking status—harm (greater recurrence and mortality) in current and benefit (lower recurrence and mortality) in never smokers. Although Touvier et al. (3) report a similar pattern, which included a benefit (of β-carotene) in never smokers, their finding lacks the rigor of the smoking interaction results of the Lung Intergroup Trial, which enjoyed the strengths of a design calling for randomization stratified by smoking status (current, former, and never) and for prespecified analyses of smoking subgroups.

While studies that examine possible interactions between nutrients/related compounds and tobacco are ongoing, what should we recommend for smokers with regard to nutrient intake? It is clear that β-carotene supplements are not advisable for current smokers, but should smokers avoid a higher dietary intake of carotenoids based on this new report? We would argue against this interpretation. Carotenoids in the diet are derived mostly from fruits and vegetables, and although there is some debate about whether total fruit and vegetable intake reduces the risk of cancer (18), no evidence shows that higher fruit and vegetable intake increases cancer risk, even in smokers (19). Moreover, increasing fruit and vegetable intake reduces the risk of cardiovascular disease in both smokers and nonsmokers, with some evidence for greater benefit in smokers (19). Therefore, the new research on the interaction between nutrients and smoking should not alter our current policy recommendations with regard to nutrients and cancer risk. Rather, this new research emphasizes the need to examine current, former, and never smokers separately in studies of nutrient supplements and other preventive agent classes in a wide spectrum of cancer prevention settings.

References


(17) Lippman SM, Lee JJ, Karp DD, Vokes EE, Benner SE, Goodman GE, et al. Randomized phase III intergroup trial of isotretinoin to prevent second...


NOTES

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