No Influence of Beta Carotene on Oxidative DNA Damage in Male Smokers

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Several large-scale human intervention studies are currently evaluating whether beta-carotene supplements may protect against cancer (1). A plausible mechanism for beta carotene could be its ability to scavenge reactive oxygen species that cause oxidative DNA damage, a crucial event in carcinogenesis (2). The most abundant base alteration induced in DNA by reactive oxygen species is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxoG) (3). In vivo this DNA base alteration is repaired by excision, and the resulting product, 8-oxoG, is excused unchanged and independently of diet into the urine. The rate of excision of 8-oxoG thus serves as a biomarker of the integrated rate of oxidative DNA damage in the whole body (4). The 8-oxoG measure has been used to demonstrate 50% higher rates of oxidative DNA damage in smokers, who have a known increased risk of cancer (4). Recently, beta carotene came into debate after a large trial in Finnish smokers did not report fewer, but rather reported even more, lung cancers following treatment with beta-carotene supplements (5).

In the present study, we have examined in a randomized intervention trial the hypothesis that supplementary beta carotene results in a reduction of oxidative DNA damage in male cigarette smokers.

The design of this trial was described previously (6). Briefly, volunteer smokers of more than 15 cigarettes per day were randomly assigned to receive either beta carotene (20 mg/day; Hoffmann-La Roche, Basel, Switzerland) or placebo treatment (10 cigarettes) for 14 weeks. The trial was approved by the external TNO Medical Ethical Committee, and each participant provided written informed consent. A total of 163 smokers (83 in the placebo group and 80 in the beta-carotene group) volunteered to participate. During the trial, 13 smokers (six in the placebo group and 80 in the beta-carotene group) discontinued participation. Blood samples were collected from all participants before and after the treatment. During week 14, urine samples were collected in week 14 by high-performance liquid chromatography with electrochemical detection as described previously (4). In 25 subjects, interfering chromatographic peaks that may have been related to recent intake of paracetamol (6) precluded analysis. In three subjects, information on creatinine analysis was missing, leaving 122 subjects (57 placebo treated and 65 beta carotene treated) for the analyses reported here.

The placebo and beta-carotene groups had comparable ages (means ± SD = 39.0 ± 10.0 years for the placebo group versus 39.3 ± 9.1 years for the beta-carotene group), body mass index (24.5 ± 2.7 kg/m² versus 24.6 ± 3.1 kg/m²), and smoking habits (20.7 ± 5.8 cigarettes per day versus 21.4 ± 5.8 cigarettes per day; 20.7 ± 10.1 years of smoking versus 21.1 ± 9.3 years of smoking) and also had similar biochemical characteristics during the trial (Table 1). Plasma creatinine levels reflect urine smoking habits. The excretion of 8-oxoG (mean ± SD) after 14 weeks was almost identical in the placebo and the beta-carotene groups, whether expressed as nanomoles per mole creatinine (2.83 ± 1.18 versus 2.98 ± 1.05, i.e., 5.6% higher in the beta-carotene group). 95% confidence interval, -0.96 to +1.99) (Fig. 1) or as total 8-oxoG excretion during the three consecutive periods (67.66 ± 32.71 nmol versus 62.25 ± 28.54 nmol).

This trial in heavy smokers shows no effect of beta carotene on oxidative DNA damage, as assessed by 8-oxoG excretion. We did not observe the 8-oxoG excretion at the beginning of the trial, but at initial difference seems improbable in our randomized design. The dose of beta carotene in this study is similar to the doses in the ongoing trials (1.5). A dose of 20 mg beta carotene per day is five to 10 times the normal intake, and plasma levels of beta carotene increased 14-fold (Table 1). Moreover, even after we excluded supplement-takers with high levels of beta carotene (~values below the median (4.13 μM/l), 8-oxoG excretion was still 8% higher (95% confidence interval, -12% to +23%). Our results indicate that there is only a 5% chance of a 7% or more reduction in 8-oxoG in the beta-carotene group.

Beta carotene has been shown to function as an antioxidant in many, but not all, in vitro systems (7). Our results suggest that beta carotene does not act as an in vivo antioxidant reducing oxidative DNA damage in humans. In smokers, beta carotene has been reported to diminish breath pentane as an index of lipid peroxidation (9), but not low-density lipoprotein oxidizability (9,10). Other antioxidants may explain the inverse associations between vegetables and cancer risk. We recently demonstrated a 2.3-fold reduction in 8-oxoG excretion after nonsmoking volunteers had consumed 300 g of Brussels sprouts for 3 weeks (11).

Our study is in line with the lack of an effect of beta carotene on lung cancer reported in Finland (12) and on colorectal adenoma reported in the United States (12). It is tempting to speculate that our...
study provides further evidence of the absence of a cancer preventive potential of beta carotene. However, the predictive value of the 8-oxodG measure for cancer development has not been established. Other studies (1,2) have shown beneficial effects of beta carotene on macular degeneration in experimentally induced macula and in macula lutea aplasia. Also, a combination of beta carotene, vitamin E, and selenium reduced smoking-related mortality in marginally nourished people in Linnian, China (1,3). Protective mechanisms for beta carotene that do not involve oxidative DNA damage may include in vivo conversion to retinoids and effects on gap-junctional communication and on metabolism of carcinogens, as well as immunomodulatory effects (1). Such a mechanism not involving oxidative DNA damage may explain the reduction of cancer incidence in men who were supplemented with beta-carotene as shown in the H axis. We did not observe a correlation 8-oxodG excretion and smoking habits (r = 0.03). Our results, using the 8-oxodG measure do not support the hypothesis that beta carotene affects cancer risk by preventing oxidative DNA damage in humans. It cannot be excluded, however, that beta carotene affects other forms of DNA damage or has other preventive mechanisms. Data from the ongoing large trials will eventually provide further information on the potential benefits of beta carotene.

References

Notes
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