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β-Carotene and Cancer Chemoprevention

Julie E. Buring, ScD[1] and Charles H. Hennekens, MD[2]

[1] Harvard Medical School, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215
[2] Harvard Medical School, Chief, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA 02215

Abstract Evidence supports the potential role of β-carotene in cancer prevention. Basic research has demonstrated that β-carotene can trap organic free radicals and/or deactivate excited oxygen molecules which may have an anticancer effect by preventing tissue damage. Although observational epidemiologic studies are not entirely consistent, many show an inverse association between dietary intake or blood levels of β-carotene and subsequent cancer risk. Two large-scale randomized trials of β-carotene have been completed. A Finnish trial demonstrated no benefit of β-carotene among middle-aged male smokers, with those assigned to this supplement in fact experiencing an increased risk of lung cancer. However, because of the long latency period for cancer, which may be a decade or more, the six-year duration of treatment in this trial may have been inadequate to detect an anticancer effect. A Chinese trial demonstrated a modest reduction in cancer mortality from a combined regimen of β-carotene, vitamin E, and selenium. The effect of the individual agents could not be assessed, and because the trial was carried out among a nutritionally deficient population, its results may not have direct relevance to well-nourished individuals. Several additional large-scale trials of β-carotene are ongoing. The Physicians' Health Study, which is testing β-carotene among 22,071 US male physicians, will have an average duration of treatment of 12.5 years at its scheduled termination in late 1995. Data in women will be available from the Women's Health Study, which began in 1992, and will randomize approximately 40,000 US female health professionals. The results from these and other ongoing trials are necessary to determine conclusively whether β-carotene reduces risks of cancer.

Key words: Antioxidants, β-carotene, chemoprevention, randomized trials

The possibility that antioxidant vitamins, including β-carotene, may prevent cancer has been the focus of considerable attention in recent years, both among the scientific research community and the general public. Cancer is one of the major causes of death in the US and most developed countries, accounting for about one-sixth of all deaths. Even the most plausible small-to-moderate benefits of β-carotene—risk reductions of 20–30%—could have a substantial public health impact. At present, however, β-carotene and other antioxidant vitamins represent a promising but unproven means to prevent cancer. This paper reviews current evidence on β-carotene and cancer, and describes ongoing large-scale randomized trials that will provide needed additional data on this question.

Address correspondence to Julie E. Buring, ScD, Associate Professor of Ambulatory Care and Prevention, Harvard Medical School, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215.

LINES OF EVIDENCE

Among the causes of cancer, diet has long been hypothesized to play an important role in etiology. Tobacco and alcohol are the two lead-

ing avoidable causes of cancer, responsible for approximately 30% and 3% of all cancer deaths, respectively. However, in their 1981 review, Doll and Peto [1] suggested that up to 35% of all malignancies may be related to dietary practices.

The antioxidant vitamin β-carotene is one constituent of diet that may play a preventive role in cancer. Basic research has outlined plausible mechanisms by which β-carotene may exert chemopreventive effects; descriptive epidemiologic studies have raised the possibility that geographic differences in cancer incidence might be explained by regional variations in intake of β-carotene, and analytic epidemiologic studies among individuals have demonstrated inverse associations between either dietary intake or blood levels of β-carotene and cancer risk. In addition, data are now available from two large-scale randomized trials testing β-carotene in cancer prevention, one in a well-nourished and another in a poorly nourished population.

OBSERVATIONAL EVIDENCE

The relationship between dietary intake of β-carotene and cancer risk has been the subject of many observational analytic studies, using both case-control and prospective cohort designs. While findings from the two types of studies are largely consistent, case-control data are subject to selection bias [2]. This review will therefore include only those observational studies of dietary intake or β-carotene blood levels that have used prospective designs.

Dietary Intake Studies of β-Carotene

Many prospective dietary studies have assessed intake of β-carotene in relation to subsequent cancer. β-Carotene, or provitamin A, is a lipid-soluble nutrient principally found in yellow, orange, and green leafy vegetables and certain fruits. Retinol deficiency causes dietary β-carotene to convert to preformed vitamin A, or retinol. If very low retinol levels are related to carcinogenesis, β-carotene could indirectly play a role in cancer prevention. In well-nourished populations, however, most dietary carotene is absorbed directly from the intestine without undergoing transformation to retinol. The possible chemopreventive benefit of β-carotene and other antioxidant vitamins relates to their ability to prevent tissue damage by trapping organic free radicals and/or deactivating excited oxygen molecules, by-products of many metabolic functions [3].

In prospective dietary studies, subjects are classified according to their reported intake of the nutrient of interest; subsequent cancer rates among those in the highest and lowest intake category are then compared. By far the largest observational study of dietary β-carotene and cancer was conducted by Hirayama and colleagues [4] in Japan. Statistically significant inverse associations were seen between β-carotene intake and cancer risk, with relative risks in the highest intake category of 0.76 for men and 0.87 for women. This cohort included over 250,000 individuals diagnosed with more than 14,000 incident cancers during a 17-year follow-up. Three other dietary studies have also reported significant inverse associations between β-carotene intake and cancer risk [5–7].

Interpreting observational dietary intake studies can be problematic; the exposure of interest may only be a marker for the true causal agent. For example, those with high β-carotene intake may smoke less or have other dietary or lifestyle practices associated with a decreased risk of cancer. Alternatively, the protection afforded by consumption of a particular food may be multifactorial, with several components of the food having chemopreventive effects. In this regard, two additional studies reported decreased risks of lung [8] and prostate [9] cancer among those with high intake of vegetables and fruits rich in both β-carotene and vitamin C. Six prospective cohort studies found no significant association between dietary β-carotene intake and subsequent overall cancer [10], as well as cancer of the colon and rectum [11], prostate [12], breast [13], lung [14], and pancreas [15].

While most dietary intake studies distinguish between vitamin A intake from β-carotene and retinol, one of the earliest analytical studies of diet and cancer related cancer risk to total vitamin A intake from all sources. The initial five-year follow-up in this cohort of 8,278 Norwegian men reported a statistically significant protective effect of high vitamin A intake on subsequent lung cancer [16]. A subsequent report from this cohort [17], which included an additional 5,480 men as well as 2,929 women, confirmed the ear-

lier finding. A recent report on breast cancer from the Nurses' Health Study, a prospective cohort investigation of more than 120,000 US women, also found a statistically significant decreased cancer risk among women with the highest intake levels of total vitamin A [13].

Blood-Based Studies of β-Carotene

In blood-based studies, blood samples are generally drawn and frozen at baseline from a cancer-free population. The study participants are followed for the subsequent development of cancer, and baseline levels of antioxidant vitamins among incident cancer cases are then compared with levels in matched controls who remained free of cancer. Although these studies are referred to as nested case-control studies, they are regarded methodologically as prospective studies, since they gather exposure information at baseline and follow subjects forward for the development of disease.

Six blood-based studies have reported significantly lower cancer risks for those in the upper category of serum or plasma β-carotene [18–23]. The most consistent pattern relates to lung malignancies, with four blood-based studies [18–20, 23] showing similar findings of an approximate halving of risk among those in the highest compared to lowest category. All of these studies controlled for the possible effects of cigarette smoking. Eight other blood-based studies have not found statistically significant associations between β-carotene levels and lower cancer risk [24–31].

Limitations of Analytic Observational Studies

While the prospective observational evidence concerning β-carotene and cancer is generally compatible with possible benefits of this agent on cancer risk, the available data are not all consistent. Additional observational data would certainly be a valuable contribution to the totality of evidence. However, regardless of the number or sample size of such investigations, or even the consistency of their findings, observational studies are unable to control for potential effects of confounding variables not known to the investigator or not collected. For example, as noted earlier, greater dietary intake of β-carotene, measured by blood levels or a diet assessment questionnaire, may only be a marker for other dietary practices that are truly protective. It is also certainly plausible that intake of β-carotene-rich foods is indeed protective, but that the benefits result from other components these foods have in common. Finally, it is possible that intake of β-carotene from food or supplements is correlated with other unmeasured or unknown nondietary lifestyle behaviors. Thus, when searching for small to moderate effects, the amount of uncontrolled confounding factors inherent in all observational studies is likely to be as large as the size of the postulated effect [2]. Because these limitations are inherent in all observational studies, only randomized trials of sufficient sample size, dose and duration of treatment and follow-up can address conclusively whether β-carotene actually decreases cancer risk.

RANDOMIZED TRIALS

Only one large-scale randomized trial has tested β-carotene in cancer prevention among a well-nourished population [32]. The recently published α-Tocopherol/β-Carotene (ATBC) Cancer Prevention Study involved six years of randomized treatment with 20 mg of β-carotene and/or 50 mg of vitamin E daily in 29,133 Finnish male smokers, aged 50–69. No protective effect on lung cancer was observed for either of the two vitamins. In fact, those assigned to β-carotene had a statistically significant 18% higher risk of lung cancer, a finding greatly at variance with the totality of other evidence suggesting a possible benefit. The chief limitation of the Finnish trial is the relatively short duration of treatment and follow-up, which may have been inadequate to yield a detectable reduction in a multistage process that often proceeds over several decades [33]. Nevertheless, the results of the Finnish trial suggest that some benefits of β-carotene seen in prior observational studies may have been overestimates, and that there may even be some previously undetected harmful effects of these vitamins.

Only one other large-scale randomized trial has assessed antioxidant vitamins in cancer prevention. The Chinese Cancer Prevention Trial randomized 29,584 residents of four communities in Linxian, a rural county in north-central China [34]. This region suffers from one of the world's

highest rates of esophageal and gastric cancer, and dietary intake of several micronutrients is very low. Nine different agents were tested (retinol, zinc, riboflavin, niacin, vitamin C, molybdenum, β-carotene, vitamin E and selenium), with trial participants assigned at random to one of eight different vitamin/mineral supplement combinations. Subjects receiving the combined treatment of β-carotene, vitamin E, and selenium had a total cancer mortality 13% lower than among those not receiving this combination, with a significant 21% decrease in gastric cancer deaths. Because nutrients were studied in combined groups, however, it is impossible to distinguish the relative contributions of β-carotene, vitamin E, or selenium to any observed finding. Moreover, vitamin supplementation may well have effects in a poorly nourished population that it would not have among those with adequate intake of the vitamins and minerals tested.

Conclusive evidence on the balance of benefits and risks of β-carotene in cancer prevention will emerge from several ongoing large-scale randomized trials among well-nourished populations. Ongoing trials of antioxidants include the "CARET" study, testing β-carotene and retinol among 18,000 individuals at high risk for lung cancer due to heavy cigarette smoking history or occupational asbestos exposure, and the SU.VI. MAX study, testing β-carotene, vitamin E, and vitamin C, as well as zinc and selenium, in healthy French men and women.

Two ongoing trials are being conducted among US health professionals. The Physicians' Health Study, begun in 1982, is testing β-carotene (50 mg on alternate days in the form of Lurotin®, supplied by BASF AG) among 22,071 US male physicians [35]. This trial will have an average treatment and follow-up duration of approximately 12.5 years at its scheduled termination in late 1995, and should therefore provide particularly reliable evidence on the potential role of β-carotene in the primary prevention of cancer. The Women's Health Study, begun in 1992, will randomize approximately 40,000 apparently healthy US women, using a 2x2x2 factorial design, to evaluate the benefits and risks of β-carotene in cancer and cardiovascular disease (50 mg on alternate days, in the form of Lurotin®, supplied by BASF AG), vitamin E (600 IU on alternate days, supplied by the Natural Source Vitamin E Association), and low-dose aspirin (100 mg on alternate days, supplied by Miles, Inc.) [36,37].

CONCLUSION

In summary, currently available data raise the possibility that β-carotene may decrease risks of cancer. At present, however, the message is not one for the general public or even for health care providers, but rather for researchers: namely, that β-carotene represents a promising but unproven means to reduce cancer risk, and should be tested in large-scale randomized trials of sufficient sample size, dose, and duration of treatment and follow-up. Evidence from such large-scale trials, including the Physicians' Health Study in men and the Women's Health Study in women, will contribute reliable data to total evidence on antioxidant vitamins, permitting appropriate clinical recommendations for individual patients, as well as a rational public health policy for the population as a whole.

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