

β-Carotene Supplementation and Incidence of Cancer and Cardiovascular Disease: the Women's Health Study

I.-Min Lee, Nancy R. Cook, JoAnn E. Manson, Julie E. Buring, Charles H. Hennekens

Background: In observational studies, individuals with high intakes of fruits and vegetables containing β-carotene experience lower risks of developing cancer. However, the few randomized trials of β-carotene supplementation show no overall benefits; some even suggest harm. This trial was designed to test the effects of β-carotene supplementation in women. **Methods:** The Women's Health Study is a randomized, double-blind, placebo-controlled trial originally testing aspirin, vitamin E, and β-carotene in the prevention of cancer and cardiovascular disease among 39 876 women aged 45 years or older. The β-carotene component was terminated early after a median treatment duration of 2.1 years (range = 0.00–2.72 years). Statistical tests were two-sided. **Results:** Among women randomly assigned to receive β-carotene (50 mg on alternate days; n = 19 939) or placebo (n = 19 937), there were no statistically significant differences in incidence of cancer, cardiovascular disease, or total mortality after a median of 4.1 years (2.1 years' treatment plus another 2.0 years' follow-up). There were 378 cancers in the β-carotene group and 369 cancers in the placebo group (relative risk [RR] = 1.03; 95% confidence interval [CI] = 0.89–1.18). There were no statistically significant differences for any site-specific cancer or during years 1 and 2 combined and years 3 and up combined. For cardiovascular disease, there were no statistically significant differences for myocardial infarction (42 in the β-carotene group versus 50 in the placebo group), stroke (61 versus 43), deaths from cardiovascular causes (14 versus 12), or the combined end point of these three events (116 versus 102; among women with more than one event, only the first was counted). Deaths from any cause were similar in the two groups (59 versus 55). Among smokers at baseline

(13% of all women), there were no statistically significant differences in overall incidence of cancer (RR = 1.11; 95% CI = 0.78–1.58) or cardiovascular disease (RR = 1.01; 95% CI = 0.62–1.63). **Conclusion:** Among apparently healthy women, there was no benefit or harm from β-carotene supplementation for a limited period on the incidence of cancer and of cardiovascular disease. [J Natl Cancer Inst 1999;91:2102–6]

Evidence from basic research and observational epidemiologic studies provides strong support for the hypothesis that persons who consume large amounts of fruits and vegetables experience lower cancer rates (1,2). Although there are many compounds in fruits and vegetables that potentially may influence cancer risk, in the 1980s the hypothesis was formulated that β-carotene may be responsible for the lower cancer rates (3). β-Carotene has antioxidant properties and may inhibit carcinogenesis by preventing DNA damage induced by free radicals (4) or by interfering with the metabolic activation of chemical carcinogens (5). It also may prevent the binding of carcinogens to DNA (6). In addition, β-carotene is converted to vitamin A in humans; the hormone-like effects of vitamin A on epithelial tissue cell growth and differentiation may inhibit the promotional stages of carcinogenesis (7). Both β-carotene and vitamin A have immunomodulatory effects and may enhance immune surveillance in carcinogenesis (8). Finally, β-carotene may enhance gap–junction communication, restricting clonal expansion of initiated cells (9).

By the mid-1990s, the findings from six trials (10–15) testing the effect of β-carotene supplementation on cancer incidence and mortality had been published. The data from these trials generally have not supported the promising findings from observational studies, and two of these trials (13,14) even suggested harm.

In this report, we provide data from another trial originally designed to test β-carotene supplementation among 39 876 apparently healthy female health professionals in the United States.

SUBJECTS AND METHODS

Study Design

The Women's Health Study was originally designed as a randomized, double-blind, placebo-controlled trial testing the balance of benefits and

risks of aspirin, vitamin E, and β-carotene in the primary prevention of cancer and cardiovascular disease, using a 2 × 2 × 2 factorial design. Written informed consent was obtained from all women before their entry into the trial. The trial was conducted after approval by the institutional review board of Brigham and Women's Hospital and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

A detailed description of the methods of the trial has been published previously (16,17). Briefly, 39 876 female health professionals, aged 45 years or older and without a history of cancer (except non-melanoma skin cancer), coronary heart disease, or cerebrovascular disease, were randomly assigned to one of the following eight treatment groups beginning in April 1993: all three active agents, three groups of two active agents and one placebo, three groups of one active agent and two placebos, or all three placebos. The active agents were 100 mg of aspirin (Bayer AG, Leverkusen, Germany) given on alternate days, 600 IU of vitamin E (Natural Source Vitamin E Association, Washington, DC) given on alternate days, and 50 mg of β-carotene (Lurotin; BASF Corporation, Wyandotte, MI) given on alternate days. A total of 19 939 women were assigned at random to receive β-carotene, and 19 937 were randomly assigned to receive placebo. The flow diagram for the β-carotene component of the trial is provided in Fig. 1. Among women assigned to receive β-carotene, 2635 (13%) were cigarette smokers at baseline; among women assigned to receive placebo, 2600 (13%) were cigarette smokers at baseline.

Following discussion with officials from the National Cancer Institute (Bethesda, MD) and the independent Data and Safety Monitoring Board of the Women's Health Study, the β-carotene component of the trial was terminated early on January 18, 1996, primarily because of the null findings on β-carotene and cancer incidence after 12 years of

Affiliations of authors: I.-M. Lee, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health, Boston, MA; N. R. Cook, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; J. E. Manson, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Department of Epidemiology, Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; J. E. Buring, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Department of Epidemiology, Harvard School of Public Health, and Department of Ambulatory Care and Prevention, Harvard Medical School; C. H. Hennekens, Department of Epidemiology and Public Health, University of Miami School of Medicine, FL.

Correspondence to: I.-Min Lee, M.B.B.S., Sc.D., 900 Commonwealth Ave. East, Boston, MA 02215 (e-mail: i-min.lee@channing.harvard.edu).

See "Notes" following "References."

© Oxford University Press

Confirmation of End Points

Women reported the occurrence of relevant end points either on their follow-up questionnaires or through letters or telephone calls. Deaths usually were reported by family members or postal authorities. We then requested written consent to review relevant medical records. Medical records were obtained from hospitals and treating physicians. Reports of cancer, cardiovascular disease, or death were considered confirmed or refuted only after review of all relevant information by an end-points committee of physicians who were blinded to treatment assignment. When consent was not provided or records could not be obtained, we did not classify that reported end point as confirmed. Medical records have been obtained and reviewed for 72% of the end points reported as of February 6, 1998. The analyses reported here are based only on confirmed end points.

For cancers that were confirmed, the vast majority (97%) were confirmed on the basis of pathology or cytology reports. Rarely, the end-points committee confirmed a reported case of cancer based on strong clinical and radiologic or laboratory marker evidence (e.g., elevated CA 125) when pathology or cytology review was not conducted. Reports of nonfatal myocardial infarction were confirmed with the use of World Health Organization criteria (19). Nonfatal stroke was defined as a typical neurologic deficit, either sudden or rapid in onset, that lasted more than 24 hours and was attributed to a cerebrovascular event. Death due to a cardiovascular cause was confirmed by convincing evidence of a cardiovascular event from all available sources, including death certificates, hospital records, and observers' accounts (for deaths occurring outside the hospital).

The primary end point of the β -carotene component of the trial was any invasive cancer (except nonmelanoma skin cancer). For the end points of cancer, myocardial infarction, and stroke, only the first occurrence in each category was counted. For cardiovascular disease, we also defined a combined end point comprising nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes; again, only the first occurrence of any of these three end points was counted.

Statistical Analysis

Cox proportional hazards regression was used to estimate the relative risk (RR) of an end point among those assigned to receive β -carotene compared with those assigned to receive placebo (20). The data were analyzed according to intention to treat, regardless of actual compliance. In our analyses, we adjusted for age and randomized treatment assignments to aspirin and vitamin E, since randomization was stratified according to these three variables. The distribution of these three variables was identical in the β -carotene and placebo groups; thus, analyses that did not adjust for these variables yielded almost identical results. For each RR, we also calculated the 95% confidence interval (CI) and two-sided *P* value. We did not adjust for other characteristics (e.g., cigarette smoking) because, as expected in this very large randomized trial, the distribution of characteristics at baseline in the β -carotene and placebo groups was virtually identical.

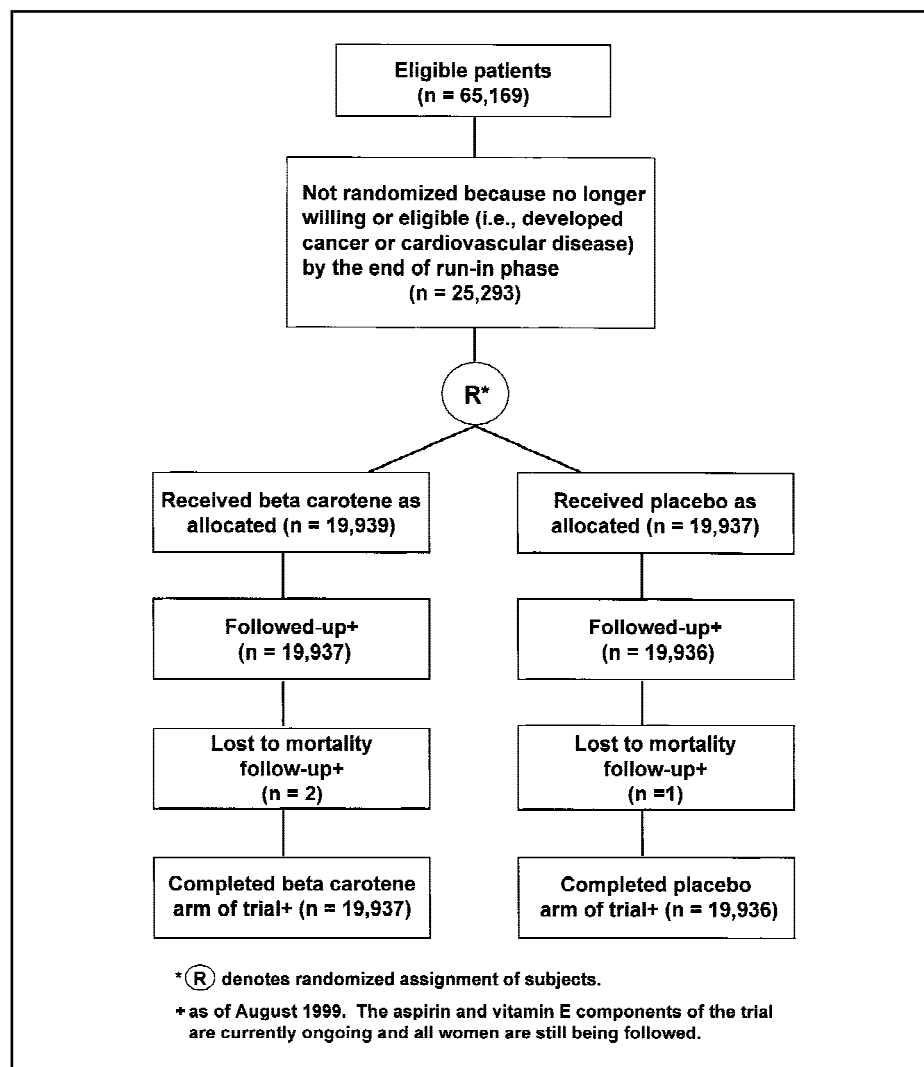


Fig. 1. Flow diagram for the β -carotene component of the Women's Health Study.

randomized treatment from a companion trial of 22 071 male health professionals in the Physicians' Health Study (15). In addition, two other trials had suggested that β -carotene may even be associated with harmful effects among individuals at high risk for lung cancer (13,14,18). The aspirin and vitamin E components of the trial presently continue uninterrupted.

Study Treatment and Follow-up

Every 6 months for the first year and annually thereafter, women received calendar packs that contained red capsules (β -carotene or placebo) on odd-numbered days and white pills (aspirin or placebo) and amber capsules (vitamin E or placebo) on even-numbered days. Every 6 months for the first year and annually thereafter, participants also were sent follow-up questionnaires that inquired about compliance with the treatment regimen and the occurrence of end points of interest as well as potential side effects. If women still had not returned a questionnaire after three mailed requests, they were telephoned to obtain information.

When the randomized β -carotene component of the trial was terminated, participants had been treated for a median of 2.1 years (range = 0.00–2.72

years). At the time of termination of the β -carotene component, 87% of the active group reported taking at least two thirds of the study capsules, while 9.9% of women in the placebo group reported taking β -carotene or vitamin A supplements outside the trial. This report includes available data as of February 6, 1998, after a median total follow-up of 4.1 years (i.e., 2.1 years' treatment plus an additional 2.0 years' follow-up). At this time, morbidity and mortality follow-up rates for 24 months (the latest completed follow-up for all women) both were 99%.

To assess whether self-reported compliance was associated with blood levels of β -carotene, we measured plasma β -carotene concentrations in blood obtained from 48 women in the Boston area during the period from September 1995 through October 1995. Appointments were scheduled 1–3 days before the visit; however, participants were unaware that blood would be drawn. Those assigned to receive β -carotene had higher plasma concentrations than those assigned to receive placebo (0.70 mg/dL versus 0.20 mg/dL; *P* < .001). Among women assigned to receive β -carotene (*n* = 25), the Spearman correlation coefficient between self-reported level of compliance and plasma β -carotene concentration was .86 (*P* = .04).

RESULTS

Cancer

As of February 6, 1998, women had been followed for a median of 4.1 years. With regard to the primary end point, 747 confirmed cases of invasive cancer had occurred—378 among women assigned to receive β -carotene and 369 among women assigned to receive placebo (Table 1). There was no statistically significant effect of β -carotene (RR = 1.03; 95% CI = 0.89–1.18).

When we examined site-specific cancers, there were no statistically significant differences in risk between women assigned to receive β -carotene and women assigned to receive placebo, even without accounting for multiple comparisons: breast (169 cases in the β -carotene group versus 168 in the placebo group), colon or rectum (34 versus 34), uterus (31 versus 27), lung (30 versus 21), ovary (24 versus 18), thyroid (nine versus 12), bladder (five versus six), brain (four versus six), pancreas (six versus four), cervix (two versus three), and stomach (one versus one). Similar numbers of melanoma (19 versus 21) and leukemia or lymphoma (17 versus 22) also occurred among women in the two groups. (The remaining 27 cases in the β -carotene group and 26 cases in the placebo group were cancers occurring at other sites or with unknown primary site.)

We then subdivided the period of risk into years 1 and 2 combined (the β -carotene component of the trial was terminated after a median treatment duration of 2.1 years) and years 3 and up combined. In neither period did we observe a statistically significant effect of β -carotene; the RR estimates were close to 1 for both periods (Table 1). For confirmed deaths due to cancer (Table 1), similar numbers occurred in the two groups (RR = 1.11; 95% CI = 0.67–1.85).

Concern has been raised that β -carotene may be harmful to current smokers. Among current smokers at baseline (2635 [13%] in the β -carotene group and 2600 [13%] in the placebo group), 64 confirmed cases of invasive cancer occurred among those assigned to receive β -carotene and 57 occurred among those assigned to receive placebo (RR = 1.11; 95% CI = 0.78–1.58). Because of the small number of smokers, we were unable to conduct meaningful analyses for site-specific cancers.

Table 1. Relative risks (RRs) and 95% confidence intervals (CIs) of cancer* according to β -carotene treatment group in the Women's Health Study

End point	β -Carotene (n = 19 939)	Placebo (n = 19 937)	RR† (95% CI)	P‡
All cancers	378	369	1.03 (0.89–1.18)	.73
Years 1 and 2 combined	219	214	1.02 (0.85–1.24)	.80
Years 3 and up combined	159	155	1.03 (0.82–1.28)	.81
Death from cancer	31	28	1.11 (0.67–1.85)	.69

*Cases of nonmelanoma skin cancer have been excluded.

†Estimates adjusted for age, randomized aspirin assignment, and randomized vitamin E assignment.

‡Two-sided test from Cox model.

Cardiovascular Events

There was no statistically significant evidence of an effect of β -carotene on myocardial infarction (42 in the β -carotene group versus 50 in the placebo group), stroke (61 versus 43), death from cardiovascular causes (14 versus 12), the combined end point of all important cardiovascular events (i.e., any of the previous three end points; among women with more than one event, only the first was counted; 116 versus 102), or death from any cause (59 versus 55) (Table 2), even without adjustment for multiple comparisons. When we subdivided the period of risk into years 1 and 2 combined and years 3 and up combined, we did not observe a statistically significant effect of β -carotene in either follow-up period.

Among current smokers at baseline (2635 [13%] in the β -carotene group and 2600 [13%] in the placebo group), 65 cases of the combined end point of all important cardiovascular events occurred during follow-up (33 in the β -carotene group versus 32 in the placebo group; RR = 1.01; 95% CI = 0.62–1.63). As with the site-specific cancers, we were unable to reliably analyze the individual

cardiovascular end points among current smokers because of small numbers.

Side Effects

As of December 3, 1998 (approximately 2 years after the β -carotene arm was terminated, allowing sufficient time for side effects to occur, reports to be collected, and the data to be processed), more women in the β -carotene group than in the placebo group reported yellowing of the skin (2131 versus 1944; $P = .003$). The prevalence of other minor side effects, such as symptoms suggestive of gastric upset or peptic ulcer, nausea, constipation, or diarrhea, did not differ between women in the two groups.

DISCUSSION

There were no overall effects of β -carotene supplementation on risk of cancer and cardiovascular disease after a median treatment duration of 2.1 years and a median total follow-up of 4.1 years in the Women's Health Study, a randomized trial conducted among 39 876 apparently healthy female health professionals throughout the United States. Specifically, we found no statistically significant benefit or harm of β -carotene treatment

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) of cardiovascular end points and total mortality according to β -carotene treatment group in the Women's Health Study

End point	β -Carotene (n = 19 939)	Placebo (n = 19 937)	RR* (95% CI)	P†
Myocardial infarction	42	50	0.84 (0.56–1.27)	.41
Stroke	61	43	1.42 (0.96–2.10)	.08
Death from cardiovascular causes	14	12	1.17 (0.54–2.53)	.69
All important cardiovascular events‡	116	102	1.14 (0.87–1.49)	.34
Years 1 and 2 combined	74	65	1.14 (0.82–1.59)	.44
Years 3 and up combined	42	37	1.14 (0.73–1.77)	.57
Death from any causes	59	55	1.07 (0.74–1.56)	.70

*Estimates adjusted for age, randomized aspirin assignment, and randomized vitamin E assignment.

†Two-sided test from Cox model.

‡A combined end point comprising nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes. Among women with more than one event, only the first was counted.

for all cancers, cardiovascular disease, or death due to any cause. For individual end points such as site-specific cancers, myocardial infarction, or stroke, we also found no statistically significant benefit or harm, although the 95% CIs for these individual end points were wider because of the smaller number of events. Among current smokers at baseline, we found no statistically significant differences between treatment groups in the overall incidence of cancer and of cardiovascular disease with the limited duration of treatment and follow-up. However, we could not provide reliable data for site-specific cancers or the individual cardiovascular events because so few women smoked cigarettes at baseline (13%).

If β -carotene truly were beneficial (or harmful), one possible explanation for our observations may have been inadequate dose or duration of treatment. The dose and formulation of β -carotene used in this study were identical to those used in the Physicians' Health Study, in which plasma β -carotene was increased approximately fourfold (21). This dose would place women in the β -carotene group in the top few percentiles of the general population with respect to usual intake and is above the level of dietary β -carotene consumption in observational studies that has been associated with benefit. Therefore, an inadequate dose of β -carotene is unlikely to explain the present null findings. In two other trials, β -carotene supplementation was associated with increased lung cancer risk. These trials used different doses and formulations of β -carotene that resulted in more than 12-fold (14) and 16-fold (13) differences in serum levels between the active treatment group and the placebo group.

Treatment duration lasted only a median of 2.1 years in the present study. In the Physicians' Health Study, no statistically significant benefit or harm with regard to cancer and cardiovascular disease emerged after 12 years of β -carotene treatment (15). Furthermore, there was no trend toward increasing benefit or harm associated with longer treatment duration. In contrast, the two trials that suggested harm among persons at high risk for lung cancer after 4 years and 5–8 years of treatment, respectively, reported no difference (14) or little difference (13) in lung cancer incidence rates between treatment and placebo groups during the first 18 months. However, after 18 months, the excess cumulative incidence of lung can-

cer in the treatment group increased progressively thereafter. Because the β -carotene component of the Women's Health Study was terminated after a median of 2.1 years, we cannot ever investigate whether the observation of no statistically significant benefit or harm would have persisted with longer term treatment.

Furthermore, given the short median total follow-up of 4.1 years, relatively few events occurred. *Post-hoc* power calculations showed that, with 746 cases of cancer, we would have 80% power to detect an RR of 0.80–0.85 associated with β -carotene (or, conversely, 1.20–1.25 if harm were expected).

Another possible explanation for these findings could have been poor compliance. However, this is unlikely, since 87% of the women in the β -carotene group were taking at least two thirds of their study pills at the time that the β -carotene component of the trial was terminated, while only 9.9% of the women in the placebo group reported taking β -carotene or vitamin A supplements outside the trial.

Bias in end-point ascertainment and confounding by other factors also are unlikely alternate explanations for the present findings. In our analyses, we considered only end points that had been confirmed by a committee of physicians who were blinded to the treatment assignment of subjects. Confounding by other factors is unlikely; as expected in this large randomized trial, the distribution of the many health habits and medical conditions about which we inquired on baseline questionnaires was balanced between the β -carotene and placebo groups. This fact makes it likely that the distribution of unmeasured and unknown confounders also is balanced.

Only one previous large trial of β -carotene has been conducted among persons at average risk for cancer. The findings from that trial, conducted among 22 071 physicians, of no statistically significant benefit or harm associated with β -carotene supplementation after 12 years (15) are similar to the findings in the present study. Another smaller trial of 1805 adults tested β -carotene in preventing recurrent skin cancers; no statistically significant effect was found after 5 years of treatment (10).

Two other large-scale trials tested β -carotene or combination regimens including β -carotene among persons at high risk for cancer. The Alpha-Tocopherol,

Beta Carotene Cancer Prevention Study (13) reported an unexpected, but statistically significant, 18% increase in lung cancer incidence after 5–8 years of treatment among male Finnish smokers assigned to receive β -carotene. The Beta-Carotene and Retinol Efficacy Trial that used a combination of high-dose β -carotene and retinyl palmitate was terminated early after 4 years, primarily as a result of its inability to detect future benefit. This trial also reported a statistically significant adverse effect, a 28% increase in lung cancer incidence, among U.S. smokers, former smokers, and workers exposed to asbestos (14). In subgroup analyses, the statistically significant increase in lung cancer incidence was seen among current smokers and among asbestos workers at baseline but not among former smokers (22).

One large trial tested a combination of β -carotene, vitamin E, and selenium in a poorly nourished Chinese population. After a treatment duration of just over 5 years, the treated group experienced a statistically significant 9% reduction in total mortality, primarily as a result of a statistically significant 21% lower stomach cancer mortality rate (11).

The reason for the apparently conflicting findings remains unclear. One possibility may be the nature of the different populations studied. In a population at average risk for cancer, β -carotene does not appear to have any statistically significant benefit or harm. Among heavy smokers, since the gas phase of cigarette smoke is highly oxidative, β -carotene in the lungs may be oxidized, yielding unstable by-products that could have pro-oxidant activity (23–25). Indirect evidence for this pro-oxidant effect was provided in a recent experiment on ferrets (26), where investigators reported that cell proliferation and squamous metaplasia were increased in the lung tissue of animals given β -carotene supplements, with further increase on exposure to tobacco smoke. In another experiment, oxidized β -carotene products enhanced the binding of carcinogens to calf thymus DNA (6). Among asbestos workers exposed to a combination of high-dose β -carotene and retinyl palmitate, asbestos fibers (which contain iron, a powerful catalyst for oxidation) present in the lungs of those with asbestosis also may promote the oxidation of β -carotene and the formation of harmful carotenoid byproducts (27). It is plausible, but unproved, that β -carotene supplementation

is harmful among such groups at high risk for lung cancer. For poorly nourished populations, β -carotene may indeed protect against cancer via the mechanisms outlined previously (4–9). In the Physicians' Health Study, among men in the lowest fourth of plasma β -carotene level at baseline, those assigned to receive active β -carotene experienced a lower risk of prostate cancer, which was statistically significant, after 12 years than those assigned to receive placebo (28).

In summary, this trial of β -carotene among apparently healthy female professionals showed no evidence of benefit or harm on cancer or cardiovascular disease after a median treatment duration of 2.1 years and a median total follow-up of 4.1 years. While the treatment duration is short, these data add to evidence suggesting that β -carotene has no statistically significant benefit or harm among persons at average risk of cancer. Since randomized trials of β -carotene supplementation probably never will be conducted again, post-treatment follow-up of these women and subjects from other trials should continue to provide information regarding long-term follow-up of subjects given β -carotene supplements for varying lengths of time.

REFERENCES

- (1) Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991;2:325–57.
- (2) Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* 1991;2:427–42.
- (3) Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;290:201–8.
- (4) Sun Y. Free radicals, antioxidant enzymes, and carcinogenesis. *Free Radic Biol Med* 1990;8: 583–99.
- (5) Bryla P, Weyand EH. Role of activated oxygen species in benzo[a]pyrene:DNA adduct formation *in vitro*. *Free Radic Biol Med* 1991;11: 17–24.
- (6) Salgo MG, Cueto R, Winston GW, Pryor WA. Beta carotene and its oxidation products have different effects on microsome mediated binding of benzo[a]pyrene to DNA. *Free Radic Biol Med* 1999;26:162–73.
- (7) Lippman SM, Meyskens FL Jr. Vitamin A derivatives in the prevention and treatment of human cancer. *J Am Coll Nutr* 1988;7:269–84.
- (8) Bendich A. Carotenoids and the immune response. *J Nutr* 1989;119:112–5.
- (9) van Poppel G. Carotenoids and cancer: an update with emphasis on human intervention studies. *Eur J Cancer* 1993;29A:1335–44.
- (10) Greenberg RE, Baron JA, Stukel TA, Stevens MM, Mandel JS, Spencer SK, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. *N Engl J Med* 1990;323:789–95.
- (11) Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;85: 1483–92.
- (12) Li JY, Taylor PR, Li B, Dawsey S, Wang GQ, Ershow AG, et al. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst* 1993; 85:1492–8.
- (13) The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029–35.
- (14) Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5.
- (15) Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145–9.
- (16) Buring JE, Hennekens CH. The Women's Health Study: rationale and background. *J Myocardial Ischemia* 1992;4:30–40.
- (17) Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. *J Myocardial Ischemia* 1992;4:27–9.
- (18) Omenn GS. Chemoprevention of lung cancer: the rise and demise of beta-carotene. *Annu Rev Public Health* 1998;19:73–99.
- (19) World Health Organization. Ischaemic heart disease registers: report of the Fifth Working Group (including a second revision of the operating protocol), Copenhagen, 26–29 April 1971. Copenhagen (Denmark): Regional Office for Europe, World Health Organization; 1971.
- (20) Cox DR. Regression models and life tables. *J Roy Stat Soc (B)* 1972;34:187–220.
- (21) Satterfield S, Greco PJ, Goldhaber SZ, Stampfer MJ, Swartz SL, Stein EA, et al. Biochemical markers of compliance in the Physicians' Health Study. *Am J Prev Med* 1990;6:290–4.
- (22) Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst* 1996;88: 1550–9.
- (23) Terao Y, Yamauchi R, Murakami H, Matsushita S. Inhibitory effects of tocopherols and beta-carotene on singlet oxygen-initiated photooxidation of methyl linoleate and soybean oil. *J Food Preserv* 1980;4:79–93.
- (24) Burton GW, Ingold KU. Beta-carotene: an unusual type of lipid antioxidant. *Science* 1984; 224:569–73.
- (25) Palozza P, Caviello G, Bartoli GM. Prooxidant activity of beta-carotene under 100% oxygen pressure in rat liver microsomes. *Free Radic Biol Med* 1995;19:887–92.
- (26) Wang XD, Liu C, Bronson RT, Smith DE, Krinsky NI, Russell M. Retinoid signaling and activator protein-1 expression in ferrets given β -carotene supplements and exposed to tobacco smoke. *J Natl Cancer Inst* 1999;91:60–6.
- (27) Cook NR, Stampfer MJ, Ma J, Manson JE, Sacks FM, Buring JE, et al. Beta carotene supplementation and total and prostate cancer incidence among randomized participants with low baseline plasma levels in the Physicians' Health Study. *Cancer* 1999;86:1783–92.
- (28) Rom WN, Bitterman PB, Rennard SI, Cantin A, Crystal RG. Characterization of the lower respiratory tract inflammation of nonsmoking individuals with interstitial lung disease associated with chronic inhalation of inorganic dusts. *Am Rev Respir Dis* 1987;136:1429–34.

NOTES

Present address: C. H. Hennekens, 1415 West Camino Real, Boca Raton, FL 33486.

Supported by Public Health Service grants CA47988 (National Cancer Institute) and HL43851 (National Heart, Lung, and Blood Institute), National Institutes of Health, Department of Health and Human Services.

We are grateful to the staff of the Women's Health Study and to the 39 876 dedicated and conscientious female health professionals who are participating in this trial.

Manuscript received May 24, 1999; revised October 7, 1999; accepted October 8, 1999.