

The New England Journal of Medicine

©Copyright, 1996, by the Massachusetts Medical Society

Volume 334

MAY 2, 1996

Number 18

LACK OF EFFECT OF LONG-TERM SUPPLEMENTATION WITH BETA CAROTENE ON THE INCIDENCE OF MALIGNANT NEOPLASMS AND CARDIOVASCULAR DISEASE

CHARLES H. HENNEKENS, M.D., JULIE E. BURING, SC.D., JOANN E. MANSON, M.D., MEIR STAMPFER, M.D., BERNARD ROSNER, PH.D., NANCY R. COOK, SC.D., CHARLENE BELANGER, M.A., FRANCES LAMOTTE, B.S., J. MICHAEL GAZIANO, M.D., PAUL M. RIDKER, M.D., WALTER WILLETT, M.D., AND RICHARD PETO, F.R.S.

Abstract Background. Observational studies suggest that people who consume more fruits and vegetables containing beta carotene have somewhat lower risks of cancer and cardiovascular disease, and earlier basic research suggested plausible mechanisms. Because large randomized trials of long duration were necessary to test this hypothesis directly, we conducted a trial of beta carotene supplementation.

Methods. In a randomized, double-blind, placebo-controlled trial of beta carotene (50 mg on alternate days), we enrolled 22,071 male physicians, 40 to 84 years of age, in the United States; 11 percent were current smokers and 39 percent were former smokers at the beginning of the study in 1982. By December 31, 1995, the scheduled end of the study, fewer than 1 percent had been lost to follow-up, and compliance was 78 percent in the group that received beta carotene.

Results. Among 11,036 physicians randomly assigned to receive beta carotene and 11,035 assigned to receive placebo, there were virtually no early or late differences in the overall incidence of malignant neoplasms or cardio-

vascular disease, or in overall mortality. In the beta carotene group, 1273 men had any malignant neoplasm (except nonmelanoma skin cancer), as compared with 1293 in the placebo group (relative risk, 0.98; 95 percent confidence interval, 0.91 to 1.06). There were also no significant differences in the number of cases of lung cancer (82 in the beta carotene group vs. 88 in the placebo group); the number of deaths from cancer (386 vs. 380), deaths from any cause (979 vs. 968), or deaths from cardiovascular disease (338 vs. 313); the number of men with myocardial infarction (468 vs. 489); the number with stroke (367 vs. 382); or the number with any one of the previous three end points (967 vs. 972). Among current and former smokers, there were also no significant early or late differences in any of these end points.

Conclusions. In this trial among healthy men, 12 years of supplementation with beta carotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes. (N Engl J Med 1996;334:1145-9.)

©1996, Massachusetts Medical Society.

OBSERVATIONAL epidemiologic studies suggest that people who consume higher dietary levels of fruits and vegetables containing beta carotene have a lower risk of certain types of cancer^{1,2} and cardiovascular disease,³ and basic research suggests plausible mechanisms.⁴⁻⁶ It is difficult to determine from observational studies, however, whether the apparent benefits are due to beta carotene itself, other nutrients in beta carotene-rich foods, other dietary habits, or other, nondietary lifestyle characteristics.⁷ Long-term, large, randomized trials can provide a direct test of the efficacy of beta

carotene in the prevention of cancer or cardiovascular disease.⁸ For cancer, such trials should ideally last longer than the latency period (at least 5 to 10 years) of many types of cancer. A trial lasting 10 or more years could allow a sufficient period of latency and an adequate number of cancers for the detection of even a small reduction in overall risk due to supplementation with beta carotene.

Two large, randomized, placebo-controlled trials in well-nourished populations (primarily cigarette smokers) have been reported. The Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study, a placebo-controlled trial, assigned 29,000 Finnish male smokers to receive beta carotene, vitamin E, both active agents, or neither, for an average of six years.⁹ The Beta-Carotene and Retinol Efficacy Trial (CARET) enrolled 18,000 men and women at high risk for lung cancer because of a history of cigarette smoking or occupational exposure to asbestos; this trial evaluated combined treatment with beta carotene and retinol for an average of less than four years.¹⁰ Both studies found no benefits of such supplementation in terms of the incidence of

From the Divisions of Preventive Medicine (C.H.H., J.E.B., J.E.M., N.R.C., C.B., F.L., J.M.G., P.M.R.) and Cardiovascular Medicine (J.M.G., P.M.R.) and the Channing Laboratory (M.S., B.R., W.W.), Department of Medicine, Brigham and Women's Hospital; the Department of Ambulatory Care and Prevention, Harvard Medical School (C.H.H., J.E.B., N.R.C.); and the Departments of Epidemiology (C.H.H., J.E.B., M.S., W.W.), Biostatistics (B.R.), and Nutrition (M.S., W.W.), Harvard School of Public Health — all in Boston; and the Imperial Cancer Research Fund Clinical Trial Service Unit, University of Oxford, Oxford, England (R.P.). Address reprint requests to Dr. Hennekens at 900 Commonwealth Ave. E., Boston, MA 02215.

Supported by grants (CA-34944, CA-40360, HL-26490, and HL-34595) from the National Institutes of Health.

cancer or cardiovascular disease; indeed, both found somewhat higher rates of lung cancer and cardiovascular disease among subjects given beta carotene. The estimated excess risks were small, and it remains unclear whether beta carotene was truly harmful. Moreover, since the duration of these studies was relatively short, they leave open the possibility that benefit, especially in terms of cancer, would become evident with longer treatment and follow-up.¹¹

In this report, we describe the findings of the beta carotene component of the Physicians' Health Study, a randomized trial in which 22,071 U.S. male physicians were treated and followed for an average of 12 years.

METHODS

Study Design

The Physicians' Health Study is a randomized, double-blind, placebo-controlled trial with a two-by-two factorial design that tested aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. The methods of the study have been described in detail previously.^{12,13} Briefly, 22,071 U.S. male physicians, who were 40 to 84 years of age in 1982 and had no history of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, or transient cerebral ischemia, were randomly assigned to one of four groups: aspirin (325 mg on alternate days [Bufferin, provided by Bristol-Myers]) plus beta carotene placebo, beta carotene (50 mg on alternate days [Lurotin, provided by BASF Corporation]) plus aspirin placebo, both active agents, or both placebos. Informed consent was obtained from all participants, and the research protocol was reviewed and approved by the institutional review board at Brigham and Women's Hospital in Boston. At base line in 1982, 11 percent of the physicians were current smokers and 39 percent were former smokers.

The randomized aspirin component of the study was terminated early, on January 25, 1988, on the advice of the external data-monitoring board, primarily because there was a statistically significant ($P < 0.001$) 44 percent reduction in the risk of a first myocardial infarction in the aspirin group.^{12,13} The randomized beta carotene component continued uninterrupted until its scheduled termination, on December 31, 1995. A total of 11,036 physicians were assigned at random to receive beta carotene and 11,035 to receive beta carotene placebo. Data on all 22,071 participants were analyzed according to their treatment assignment, regardless of subsequent compliance.

Study Treatment and Follow-up

Every six months for the first year and annually thereafter, the participants were sent monthly calendar packs (provided by Bristol-Myers from 1982 through 1988) that contained red capsules (beta carotene or placebo) for even-numbered days and white pills (aspirin or placebo) for odd-numbered days. After January 25, 1988, physicians could request that their white pills be active aspirin, but the beta carotene component of the trial remained randomized, double-blind, and placebo-controlled until December 31, 1995. Participants were sent brief yearly follow-up questionnaires, asking about their compliance with the treatment regimen and about the occurrence of any relevant events. After three mailed requests for follow-up information, the participants were contacted by telephone. When the randomized aspirin study was terminated, participants had been treated for an average of five years; 99.7 percent were providing follow-up with respect to morbidity by mailed questionnaire or telephone interview; follow-up for mortality was 100 percent complete. At the time, 85 percent of the beta carotene group was still taking the study pills; in the placebo group, 4 percent reported taking beta carotene or vitamin A supplements.

By the end of 1995, participants had been taking beta carotene or placebo for an average of 12 years (range, 11.6 to 14.2). At the end of 11 years of follow-up (the last year completed for all participants), 99.2 percent were still providing information on morbidity; follow-up for mortality was 99.99 percent complete. In both the beta carotene

group and the placebo group, 80 percent of participants were still taking the study pills, with an average compliance of over 97 percent. The remaining 20 percent were not taking any study pills. Thus, in the beta carotene group, 78 percent of the study pills were reported as still being taken; in the placebo group, 6 percent of the physicians reported taking supplemental beta carotene or vitamin A.

To assess the validity of reported compliance with the assigned treatment, we measured plasma beta carotene concentrations in blood obtained at unannounced visits to study participants' offices in three geographic areas.¹⁴ Those assigned to receive beta carotene had significantly higher concentrations than those given placebo (1.2 vs. 0.3 mg per liter [2.24 vs. 0.56 mmol per liter], $P < 0.001$). Only one participant assigned to the placebo group had a plasma beta carotene concentration equal to the mean in the beta carotene group, and he reported taking a beta carotene supplement. In addition, there was a highly significant correlation between the subjects' reports of their compliance with the study regimen and their plasma beta carotene concentrations ($r = 0.69$, $P < 0.001$).

Confirmation of End Points

When a relevant end point was reported, we requested written consent to review the participant's medical records. Details were requested from hospitals and treating physicians. Reports of malignant neoplasms, cardiovascular disease, or death were considered refuted or confirmed only after the examination of all available information by an end-points committee made up of two internists, a cardiologist, and a neurologist, all of whom were blinded to the treatment assignments. When written consent or the relevant records could not be obtained, a reported event was not classified as confirmed. So far, medical records have been obtained and reviewed for over 95 percent of the events reported as of October 24, 1995. Unless otherwise indicated, the analyses reported here for the main end points include all events that have not been refuted by review of the medical records, since most of the events reported by participating doctors will eventually be confirmed. In fact, 95 percent of the events that have not been refuted have so far been confirmed. Furthermore, all analyses were repeated with only confirmed events included, and the results were virtually identical to those without the exclusion of events not yet confirmed for all time periods. (We have also presented data on major end points based only on confirmed events.)

Reported cases of malignant neoplasm required confirmation by pathology report. Diagnoses of nonfatal myocardial infarction were confirmed with the use of World Health Organization criteria.¹⁵ 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 mechanism from available sources, including death certificates, hospital records, and (for death outside the hospital) observers' accounts.

The primary end point for the beta carotene component of the trial was any type of malignant neoplasm except nonmelanoma skin cancer. Malignant neoplasms diagnosed within two years of randomization were considered separately, as specified in advance, since many of these may have been present as preclinical disease at base line. For the end points of malignant neoplasm, myocardial infarction, and stroke, only the first end point in each category reported by a participant was counted. For example, if a participant reported having a malignant neoplasm, no subsequently diagnosed case was counted in the analyses of total malignant neoplasms, although that physician continued to be followed for cardiovascular disease and mortality.

Statistical Analysis

The Cox proportional-hazards model was used to estimate the relative risk of an end point among those randomly assigned to beta carotene as compared with those assigned to placebo, with adjustment for age at base line and, during the first five years, random assignment to the aspirin or placebo group in the aspirin component of the trial. Controlling for assignment with respect to aspirin did not change the estimates of relative risk, nor did the participants' assignment with respect to aspirin materially alter the effect of beta carotene on any of the primary end points. For each relative risk, the 95 percent confidence interval and two-sided P value were calculated. As

expected in a large, randomized trial, the distribution of base-line characteristics was virtually identical in the beta carotene and placebo groups.¹⁶

RESULTS

Malignant Neoplasms

As shown in Table 1 and Figure 1, after an average of 12 years of treatment and follow-up, there was no significant effect of beta carotene on the primary end point of all cases of malignant neoplasm (1273 cases in the beta carotene group vs. 1293 in the placebo group; relative risk, 0.98; 95 percent confidence interval, 0.91 to 1.06). When the period of risk was subdivided according to years of follow-up, there was still no statistically significant benefit or harm, even after five or more years of treatment and follow-up. When these analyses were repeated with only confirmed events included, the relative risks were virtually identical for all time periods, including five or more years (Table 1).

Similarly, there was no statistically significant benefit or harm due to beta carotene with respect to cancer of the lung (82 cases in the beta carotene group vs. 88 in the placebo group), colon and rectum (167 vs. 174), prostate (520 vs. 527), stomach (19 vs. 21), pancreas (29 vs. 21), or brain (25 vs. 31) or for melanoma (64 vs. 73), leukemia (35 vs. 42), or lymphoma (86 vs. 80). With respect to bladder cancer, there were 62 cases in the beta carotene group and 41 in the placebo group; with respect to thyroid cancer, there were 16 in the beta carotene group and 2 in the placebo group. After adjustment for multiple comparisons, however, neither of these differences was statistically significant at the 0.05 level. In fact, previous observational studies of bladder cancer¹⁷ and thyroid cancer¹⁸ had suggested a possible protective effect of foods rich in beta carotene. There was no significant effect of beta carotene on the number of deaths due to all malignant neoplasms (386 vs. 380) (Table 1) or deaths due to lung cancer (63 vs. 62).

Cardiovascular Events

There was no statistically significant benefit or harm from beta carotene with respect to the number of myocardial infarctions (468 in the beta carotene group vs. 489 in the placebo group), strokes (367 vs. 382), deaths due to cardiovascular causes (338 vs. 313), all important cardiovascular events (967 vs. 972), or deaths from all causes (979 vs. 968) (Table 2 and Fig. 1). Moreover, there was no significant trend toward greater benefit or harm with an increasing duration of treatment, even five or more years after randomization.

Effects among Smokers

Although the ATBC and CARET studies raised the possibility that beta carotene might cause harm in current smokers, the relative risk of all malignant neoplasms for participants in the Physicians' Health Study who were smokers in 1982 was 1.05 for the beta carotene group as compared with the placebo group (95 percent confidence interval, 0.86 to 1.28); that of lung cancer, 0.90 (95 percent confidence interval, 0.58 to

Table 1. Cases of Malignant Neoplasm in the Beta Carotene Component of the Physicians' Health Study, According to Treatment Group and Years of Follow-up.*

END POINT	BETA CAROTENE (N = 11,036)	PLACEBO (N = 11,035)	RELATIVE RISK (95% CI)	P VALUE
Malignant neoplasm†	1273	1293	0.98 (0.91–1.06)	0.65
Yr 1–4	277	266	1.04 (0.88–1.23)	0.64
Yr 1–2	120	130	0.92 (0.72–1.18)	0.52
Yr 3–4	157	136	1.16 (0.92–1.45)	0.22
Yr 5–9	500	567	0.88 (0.78–0.99)	0.03
Yr ≥10	496	460	1.08 (0.95–1.22)	0.25
Malignant neoplasm in yr ≥3	1153	1163	0.99 (0.91–1.07)	0.79
Death due to malignant neoplasm	386	380	1.02 (0.89–1.18)	0.76

*All events reported by the participants and not refuted by review of medical records are included. Cases of nonmelanoma skin cancer have been excluded. Relative risks have been adjusted for age and random assignment in the aspirin component of the trial. CI denotes confidence interval.

†Of the 2566 malignant neoplasms, 2426 have so far been confirmed (1202 in the beta carotene group and 1224 in the placebo group). These include 534 in years 1 through 4 (272 vs. 262), 1048 in years 5 through 9 (492 vs. 556), and 844 in year 10 or later (438 vs. 406).

1.40); that of death from cardiovascular causes, 1.13 (95 percent confidence interval, 0.80 to 1.61); and that of death from all causes, 1.05 (95 percent confidence interval, 0.86 to 1.29) (Table 3).

Side Effects

During 12 years of treatment and follow-up, no major side effects were significantly associated with assignment to beta carotene supplementation. Minor side effects included statistically significant increases in reports of yellowing of the skin (which occurred in 1745 subjects in the beta carotene group as compared with 1535 in the placebo group) and minor gastrointestinal symptoms, such as belching associated with the red capsules (275 vs. 124), findings described previously in studies of beta carotene in this dose and formulation.¹⁹

DISCUSSION

This large-scale, randomized trial among apparently healthy, well-nourished men demonstrated no statistically significant benefit or harm due to 12 years of beta carotene supplementation in terms of malignant neoplasms, cardiovascular disease, or death. Because of the long duration of the trial, these findings are particularly informative, and the large sample and narrow confidence intervals exclude even a small overall benefit or harm due to beta carotene with a high degree of assurance. However, for individual end points such as stroke, myocardial infarction, and particular types of cancer, the confidence intervals are wider and do not preclude the possibility of a small absolute effect. In view of the slow development of many cancers, follow-up in this and the other trials of beta carotene will continue even though treatment has ceased, in case any benefits or hazards become clear later.

Factors that could, at least in theory, have produced a false finding of no benefit or harm include an inadequate dose of beta carotene or poor compliance with the assigned treatment. The dose of beta carotene used

in the trial, however, placed participants in the top few percentiles of the general population with respect to usual intake, while minimizing noticeable yellowing of the skin. In our studies of the bioavailability of beta carotene, this alternate-day dosage and formulation increased plasma beta carotene concentrations approximately fourfold.¹⁴ This intake is above the level of dietary beta carotene consumption that is associated with benefit in observational studies and is roughly equivalent in effects on blood levels to about two carrots a day (as compared with about three carrots a day in the ATBC study and four carrots a day in CARET). Poor compliance (either the failure of those assigned to receive beta carotene to adhere to the study treatment or the use of beta carotene supplements by those assigned to the placebo group) is not a plausible explanation for our findings, since there was 85 percent compliance with beta carotene treatment after 5 years and compliance was still 78 percent after 12 years; in addition, the use of beta carotene or vitamin A supplements was reported by only 6 percent of the placebo group even by the end of the trial.

Observation bias is an unlikely explanation for our findings, since reports of end points were refuted or confirmed by a committee of physicians blinded to the participants' treatment assignments, and separate analyses of unrefuted and confirmed events gave virtually identical results.

Two other large trials of beta carotene or combination treatments incorporating beta carotene in well-nourished populations^{9,10} and one in a poorly nourished population²⁰ have been conducted, but they involved only four to six years of treatment, with no post-treatment results yet available. One reported a significant benefit of beta carotene,²⁰ whereas two found that it had significant adverse effects with respect to cancer

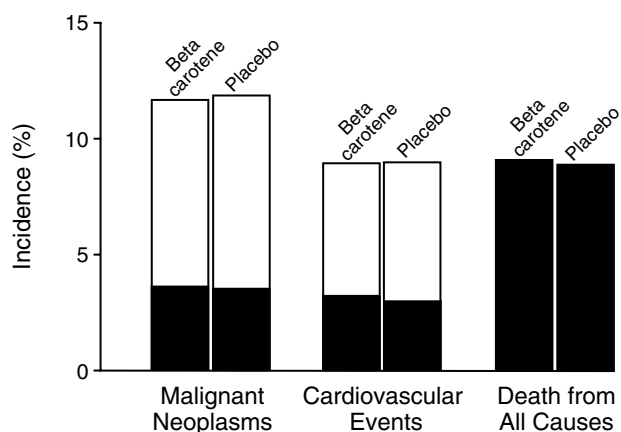


Figure 1. Incidence of Malignant Neoplasms, Cardiovascular Events, and Death from All Causes in the Beta Carotene and Placebo Groups.

All types of malignant neoplasm except nonmelanoma skin cancer are included. Cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes. The shaded areas indicate deaths.

Table 2. Cardiovascular End Points and Total Mortality in the Beta Carotene Component of the Physicians' Health Study, According to Treatment Group.*

END POINT	BETA CAROTENE (N = 11,036)	PLACEBO (N = 11,035)	RELATIVE RISK (95% CI)	P VALUE
Myocardial infarction	468	489	0.96 (0.84–1.09)	0.50
Stroke	367	382	0.96 (0.83–1.11)	0.60
Death from cardiovascular causes	338	313	1.09 (0.93–1.27)	0.28
All important cardiovascular events†	967	972	1.00 (0.91–1.09)	0.90
Yr 1–4	259	283	0.91 (0.77–1.08)	0.29
Yr 1–2	130	157	0.83 (0.66–1.04)	0.11
Yr 3–4	129	126	1.02 (0.80–1.30)	0.87
Yr 5–9	396	375	1.06 (0.92–1.22)	0.46
Yr ≥10	312	314	1.00 (0.85–1.16)	0.95
Death from all causes	979	968	1.02 (0.93–1.11)	0.68

*All events reported by the participants and not refuted by review of medical records are included. Relative risks have been adjusted for age and random assignment in the aspirin component of the trial. CI denotes confidence interval.

†A combined end point comprising nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes. Of the 1939 events, 1837 have so far been confirmed (908 in the beta carotene group and 929 in the placebo group). These include 536 in years 1 through 4 (255 vs. 281), 765 in years 5 through 9 (392 vs. 373), and 536 in year 10 or later (261 vs. 275).

rates in the first few years.^{9,10} In our trial, however, we found no evidence either of benefit or of increased risk associated with beta carotene, even in the later period. There were 996 malignant neoplasms diagnosed five or more years after randomization in the beta carotene group, and 1027 in the placebo group. The absence of a significant effect on cancer rates in the later part of the study suggests that beta carotene supplements are likely to have little or no effect on cancer rates in the first few years after randomization.

Furthermore, the finding in the two other large trials of possible harm among smokers given beta carotene^{9,10} is not consistent with the results of observational studies, which have, in fact, suggested that fruits and vegetables rich in beta carotene may prevent lung cancer^{21,22} and coronary heart disease²³ in smokers. Although, in the Physicians' Health Study, participants who were cigarette smokers in 1982 represented only 11 percent and former smokers only 39 percent of the total, those assigned to receive beta carotene supplements had no statistically significant decrease or increase in risks.

In addition to these four large-scale trials, two smaller trials of beta carotene supplementation in the prevention of recurrent skin cancer¹⁹ and colon polyps²⁴ have also been completed. Both found that beta carotene had no significant benefit or harm.

Our chief aim in this trial was to provide either a definitive positive result or an informative null finding on which to base rational public health recommendations. The need for such reliable evidence is underscored by the fact that a substantial amount of money is spent on beta carotene supplements by the general public. Even though beta carotene is ineffective in preventing cancer and cardiovascular disease, other micronutrients may not be. For example, vitamin E supplementation remains promising as a preventive intervention.^{3,23,25} It is

Table 3. End Points in the Beta Carotene Component of the Physicians' Health Study, According to Treatment Group and Smoking Status at Base Line.*

END POINT AND SMOKING STATUS	BETA CAROTENE (N = 11,036)	PLACEBO (N = 11,035)	RELATIVE RISK (95% CI)	P VALUE
Malignant neoplasm†				
Nonsmoker	511	521	0.99 (0.88–1.12)	0.88
Former smoker	560	583	0.95 (0.84–1.06)	0.36
Current smoker	201	186	1.05 (0.86–1.28)	0.65
Lung cancer				
Nonsmoker	10	13	0.78 (0.34–1.79)	0.56
Former smoker	34	33	1.00 (0.62–1.61)	0.99
Current smoker	38	41	0.90 (0.58–1.40)	0.63
Death due to malignant neoplasm				
Nonsmoker	131	137	0.98 (0.77–1.25)	0.89
Former smoker	171	175	0.96 (0.78–1.19)	0.73
Current smoker	84	67	1.23 (0.89–1.69)	0.21
Myocardial infarction				
Nonsmoker	189	218	0.88 (0.72–1.07)	0.19
Former smoker	194	194	1.00 (0.82–1.22)	0.97
Current smoker	84	76	1.08 (0.80–1.48)	0.61
Stroke				
Nonsmoker	140	156	0.92 (0.73–1.16)	0.48
Former smoker	154	166	0.90 (0.72–1.12)	0.35
Current smoker	70	59	1.18 (0.83–1.67)	0.35
Death from cardiovascular causes				
Nonsmoker	121	126	1.00 (0.78–1.29)	0.99
Former smoker	148	126	1.16 (0.92–1.48)	0.21
Current smoker	67	58	1.13 (0.80–1.61)	0.50
All important cardiovascular events				
Nonsmoker	376	414	0.92 (0.80–1.06)	0.26
Former smoker	405	397	1.00 (0.87–1.15)	0.96
Current smoker	182	157	1.15 (0.93–1.43)	0.19
Death from all causes				
Nonsmoker	361	361	1.03 (0.89–1.20)	0.66
Former smoker	423	423	0.98 (0.86–1.13)	0.82
Current smoker	192	179	1.05 (0.86–1.29)	0.64

*All events reported by participants and not refuted by review of medical records are included. Relative risks have been adjusted for age and random assignment in the aspirin component of the trial. CI denotes confidence interval. At base line, 10,919 (49 percent) of the participants had never smoked, 8674 (39 percent) were former smokers, 2438 (11 percent) were current smokers, and 40 (0.2 percent) could not be classified.

†Excluding nonmelanoma skin cancer.

currently being tested in a large-scale primary-prevention trial among women²⁶ and in several trials among people at high risk.²⁷ For beta carotene, however, the results of this trial indicate that supplementation is not effective in preventing cancer or cardiovascular disease in apparently healthy, well-nourished men.

We are indebted to the 22,071 study physicians for their dedicated and conscientious collaboration; to the staff of the Physicians' Health Study, particularly Allison Blodgett, Beth Breen, Kenneth Breen, Mary Breen, Michael Jonas, Patrick McCormack, Geneva McNair, Leslie Power, Joanne Crowley Smith, Ayn Stampfer, Miriam Schwartz, M.D., Michelle Sheehy, Martin Van Denburgh, and Phyllis Johnson Wojciechowski; and to the BASF Corporation and Bristol-Myers Products for their logistic support.

APPENDIX

The members of the End Points Committee were S. Goldhaber, C. Kase, M. Stampfer, and J. Taylor (chairman). The members of the Data Safety and Monitoring Board were L. Cohen, R. Collins, D. DeMets (chairman), I.C. Henderson, A. LaCroix, and R. Pren-

tice. Ex officio members were F. Ferris, L. Friedman, P. Greenwald, N. Kurinij, M. Perloff, and E. Schron.

REFERENCES

- Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;290:201-8.
- Buring JE, Hennekens CH. Retinoids and carotenoids. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 4th ed. Philadelphia: J.B. Lippincott, 1993:464-74.
- Gaziano JM, Manson JE, Buring JE, Hennekens CH. Dietary antioxidants and cardiovascular disease. *Ann N Y Acad Sci* 1992;669:249-59.
- Burton GW, Ingold KU. Beta-carotene: an unusual type of lipid antioxidant. *Science* 1984;224:569-73.
- Stich HF, Rosin MP, Vallejera MO. Reduction with vitamin A and beta-carotene administration of proportion of micronucleated buccal mucosal cells in Asian betel nut and tobacco chewers. *Lancet* 1984;1:1204-6.
- Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989;320:915-24.
- Hennekens CH, Buring JE. Observational evidence. *Ann N Y Acad Sci* 1993;703:18-24.
- Idem*. *Epidemiology in medicine*. Boston: Little, Brown, 1987.
- 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.
- Omenn GS, Goodman GE, Thornquist MD, 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.
- Hennekens CH, Buring JE, Peto R. Antioxidant vitamins — benefits not yet proven. *N Engl J Med* 1994;330:1080-1.
- The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1988;318:262-4.
- Idem*. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129-35.
- Satterfield S, Greco PJ, Goldhaber SZ, et al. Biochemical markers of compliance in the Physicians' Health Study. *Am J Prev Med* 1990;6:290-4.
- 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.
- Manson JE, Buring JE, Satterfield S, Hennekens CH. Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians. *Am J Prev Med* 1991;7:150-4.
- Nomura AMY, Kolonel LN, Hankin JH, Yoshizawa CN. Dietary factors in cancer of the lower urinary tract. *Int J Cancer* 1991;48:199-205.
- Franceschi S, Levi F, Negri E, Fassina A, La Vecchia C. Diet and thyroid cancer: a pooled analysis of four European case-control studies. *Int J Cancer* 1991;48:395-8.
- Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. *N Engl J Med* 1990;323:789-95. [Erratum, *N Engl J Med* 1991;325:1324.]
- Blot WJ, Li J-Y, Taylor PR, 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.
- Menkes MS, Comstock GW, Vuilleumier JP, Helsing KJ, Rider AA, Brookmeyer R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *N Engl J Med* 1986;315:1250-4.
- Hennekens CH. Micronutrients and cancer prevention. *N Engl J Med* 1986;315:1288-9.
- Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;328:1450-6.
- Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 1994;331:141-7.
- Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med* 1993;328:1444-9.
- Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. *J Myocardial Ischemia* 1992;4(5):27-9.
- Gaziano JM, Manson JE, Hennekens CH. Natural antioxidants and cardiovascular disease: observational epidemiologic studies and randomized trials. In: Frei B, ed. *Natural antioxidants in human health and disease*. San Diego, Calif.: Academic Press, 1994:387-409.