

EFFECTS OF A COMBINATION OF BETA CAROTENE AND VITAMIN A ON LUNG CANCER AND CARDIOVASCULAR DISEASE

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Abstract *Background.* Lung cancer and cardiovascular disease are major causes of death in the United States. It has been proposed that carotenoids and retinoids are agents that may prevent these disorders.

Methods. We conducted a multicenter, randomized, double-blind, placebo-controlled primary prevention trial — the Beta-Carotene and Retinol Efficacy Trial — involving a total of 18,314 smokers, former smokers, and workers exposed to asbestos. The effects of a combination of 30 mg of beta carotene per day and 25,000 IU of retinol (vitamin A) in the form of retinyl palmitate per day on the primary end point, the incidence of lung cancer, were compared with those of placebo.

Results. A total of 388 new cases of lung cancer were diagnosed during the 73,135 person-years of follow-up (mean length of follow-up, 4.0 years). The active-treatment group had a relative risk of lung cancer of 1.28 (95 percent confidence interval, 1.04 to 1.57; $P=0.02$), as

compared with the placebo group. There were no statistically significant differences in the risks of other types of cancer. In the active-treatment group, the relative risk of death from any cause was 1.17 (95 percent confidence interval, 1.03 to 1.33); of death from lung cancer, 1.46 (95 percent confidence interval, 1.07 to 2.00); and of death from cardiovascular disease, 1.26 (95 percent confidence interval, 0.99 to 1.61). On the basis of these findings, the randomized trial was stopped 21 months earlier than planned; follow-up will continue for another 5 years.

Conclusions. After an average of four years of supplementation, the combination of beta carotene and vitamin A had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, cardiovascular disease, and any cause in smokers and workers exposed to asbestos. (N Engl J Med 1996;334:1150-5.)

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LUNG cancer is the leading cause of death from cancer in the United States, accounting for approximately 29 percent of deaths from cancer and 6 percent of all deaths.¹ New approaches are essential to prevent lung cancer in persons who have smoked cigarettes or who have had occupational exposure to asbestos. Twenty-nine percent of men and 25 percent of women who are 45 to 64 years of age currently smoke,² and at least 40 percent of men and 20 percent of women in this age group are former smokers.³ An estimated 4000 to 6000 deaths from lung cancer per year are attributed to exposure to asbestos.^{4,5}

On the basis of epidemiologic observations and laboratory studies, beta carotene and vitamin A have attracted wide interest as agents that may prevent lung cancer.⁶⁻⁹ The Beta-Carotene and Retinol Efficacy Trial (CARET) is one of several recent trials to assess the

chemopreventive efficacy and safety of beta carotene and related agents.¹⁰⁻¹³

This report presents interim efficacy results of the CARET study, which coincided with the announcement of the steering committee's decision on January 11, 1996, to stop the trial's active intervention. Follow-up for additional end points is expected to continue for another five years.

METHODS

Study Design

The study's strategy, design, detailed methods, eligibility, pilot-study findings, and recruitment information have been published elsewhere.^{9,14-16} Briefly, CARET was organized in 1983 and began randomization in Seattle in 1985 in two pilot studies: one enrolled 816 men with substantial occupational exposure to asbestos, who were randomly assigned in a 1:1 ratio to receive either a combination of 15 mg of beta carotene per day and 25,000 IU of retinol per day (active treatment) or placebo; the second enrolled 1029 men and women with extensive histories of cigarette smoking, to receive 30 mg of beta carotene per day, 25,000 IU of retinol per day, both vitamins, or neither vitamin (two-by-two design). The trial was expanded to include additional study centers in 1988 and 1991, and all subjects were randomly assigned in a 1:1 ratio to either active treatment or placebo. The pilot groups receiving active agents were consolidated in 1988 into a single group receiving a standard daily regimen of 30 mg of beta carotene plus 25,000 IU of retinol in the form of retinyl palmitate. Thus, in the pilot study with the cohort of smokers, three subjects were assigned to active treatment for every subject assigned to placebo; therefore, the rates rather than numbers of end points must be compared between active and placebo groups. The design¹⁴ called for active intervention until late 1997 (110,000 person-years), with reporting of results in 1998.

Eligibility, Recruitment, and Randomization

Workers exposed to asbestos were men 45 to 74 years of age in the pilot study and 45 to 69 years of age in the later period of re-

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Supported by grants (U01 CA63673, U01 CA63674, U01 CA47989, U01 CA48200, U01 CA48203, U01 CA48196, and U01 CA52596) from the National Cancer Institute.

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cruitment. To be eligible for the study the subjects had to have first been exposed to asbestos on the job 15 years before randomization, and either have had a chest x-ray film positive for asbestos-related lung disease or have worked in specified high-risk trades — as plumbers and pipe fitters, steamfitters, shipyard boilermakers, non-shipyard boilermakers, shipyard electricians, ship scalers, insulators, plasterboard workers, or sheet-metal workers — for 5 years. The asbestos pilot study had no requirements regarding smoking¹⁵; subsequently, subjects were required to be current smokers or to have smoked within the previous 15 years. For the population of smokers, women and men were recruited from health insurance rolls and managed-care organizations if they were 50 to 69 years of age, had at least 20 pack-years of cigarette smoking, and either were currently smoking or had quit smoking within the previous six years. The participants agreed to limit their supplemental intake of vitamin A to less than 5500 IU per day and to take no supplemental beta carotene. A total of 4060 workers exposed to asbestos and 14,254 heavy smokers (44 percent of whom were women) were randomized. We provided detailed information for informed consent at recruitment and regularly thereafter, including a letter to each participant describing the results of the 1994 Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC).¹⁰

Active agents and placebos were purchased from Hoffmann-LaRoche and formulated by Tishcon Corporation. Both formulations were given as capsules. Beta carotene beadlets were combined with retinyl palmitate in a single capsule and dispensed in bottles, which were weighed and their contents checked. We assessed the subjects' compliance by weighing the returned bottles to estimate the number of capsules remaining (in 85 percent of the assessments) or by relying on the subjects' own estimates (15 percent). Blood was collected annually from the original pilot participants and every two years from the other participants.

Subjects who stopped receiving study vitamins for any reason other than death were defined as inactive participants and were still followed for end points and counted in the analyses.

Data Collection and Monitoring of Safety and End Points

Each year active participants visited a study center once and were telephoned twice, at four-month intervals. Inactive participants were telephoned semiannually. Over 97 percent of scheduled contacts were completed. As of December 15, 1995, ascertainment of vital status was more than 98 percent complete.

Symptoms and signs and newly diagnosed medical conditions were monitored closely by questionnaire at all contacts and in limited physical examinations during study-center visits; laboratory values for liver function and serum analytes were monitored annually in participants randomized in the pilot studies (for use in adjusting estimates of relative risk with the case-cohort approach).¹⁷ The 13 monitored symptoms were graded according to the CARET symptom-assessment scale.¹⁶ An independent safety and end-points monitoring committee met semiannually to review in blinded fashion data coded according to intervention group. When the results of the ATBC Cancer Prevention trial¹⁰ became available, the committee reviewed the results of the first interim analysis and requested that the blinding be ended. Subsequently, the committee reviewed data unblinded.

Ascertainment and Evaluation of End Points

All initial reports of cancers and deaths from each study center were submitted to the coordinating center and entered into a tracking system. Participants and all study staff members involved in the ascertainment and evaluation of end points and assignment of final diagnoses remained unaware of the participants' treatment assignment throughout the trial. Clinical records and, for tumors involving the lung, pathology specimens were obtained for independent review by the end-points review committee, composed of two oncologists, two internists, and a pathologist. An end point was considered confirmed when the end-point review process was completed. Through December 15, 1995, a total of 2420 end points had been reported: 1446 cancers (in 1353 participants) and 974 deaths. Of the initial reports of

lung cancer for which the end-point-review process was completed, 90 percent were confirmed; most of the remainder were found to be metastases and recurrences.

Statistical Analysis

The primary analysis, based on the intention to treat, was designed to test for differences between treatment groups in the incidence of lung cancer with a weighted log-rank statistic stratified according to the risk group (workers exposed to asbestos or heavy smokers), time of recruitment (pilot study or subsequent period), and study center (six centers).¹⁴ Parameter estimates and the results of statistical tests were similar with and without the weighting; we present here the unweighted results. Estimates of relative risk and confidence intervals were obtained from stratified Cox regression models with the same strata as the log-rank statistics. The cumulative incidence of end points was plotted through 5½ years of follow-up because of the small number of participants beyond that time and involved 354 participants with new cases of lung cancer, 829 deaths, and 67,449 person-years of follow-up. Follow-up for all participants began at randomization.

The prespecified monitoring policy for stopping the trial early because of a benefit or adverse effect of the study vitamins was based on O'Brien-Fleming boundaries¹⁸ applied to the weighted number of confirmed lung-cancer end points, the primary end point. The critical P values were those of 0.0006 or lower for the first interim analysis in 1994 and those of 0.007 or lower for the second interim analysis in 1995. Results are based on active intervention through December 15, 1995, at which time the 18,314 participants had accumulated 73,135 person-years of follow-up (mean, 4.0 years; median, 3.7).

RESULTS

Characteristics of the Participants

The two randomized groups were well matched, with a high-risk profile for lung cancer and cardiovascular disease in both the smokers and the workers exposed to asbestos (Table 1). All smokers were encouraged and assisted, if willing, to stop smoking, and all former smokers were encouraged to maintain that status. Among current smokers, there was a net smoking-cessation rate of 5 percent per year.

Through December 15, 1995, 15 percent of the workers exposed to asbestos who were assigned to active treatment became inactive participants, as compared with 14 percent of those assigned to placebo. The respective values in the group of heavy smokers were 20 percent and 19 percent. Among the active participants, the mean rates of capsule consumption were 93 percent through five years of follow-up, with no significant differences between treatment groups. The percentage of participants who took non-study-related supplemental beta carotene or vitamin A in doses of more than 5500 IU per day was low (2 percent and 1 percent, respectively). After five years of study supplementation, the median serum beta carotene concentration in the active-treatment group was 2100 ng per milliliter, as compared with 170 ng per milliliter in the placebo group; serum retinol levels were about 10 percent higher than those in the placebo group ($P < 0.01$). Except for slight skin yellowing in some of those receiving beta carotene (0.3 percent had yellowing of grade 3 or higher on the CARET symptom-assessment scale),¹⁶ there were no differences of clinical importance between groups in any of the 13 monitored symp-

toms and signs, in tests of liver function, or in newly diagnosed conditions.

Incidence of Lung Cancer

The incidence of lung cancer was the primary end point. Through December 15, 1995, 388 participants — 2 percent of the total — were reported to have new cases of lung cancer (5.4 per 1000 person-years). In the case of 286, the end points were confirmed, whereas in the case of 102, further review by the end-points committee was pending. Among the 388, 254 had died. Five participants had two primary lung cancers each. The 388 participants represent 79 percent of the 490 participants projected in our statistical design to have lung cancer by the end of the intervention. The 73,135 person-years of follow-up accrued correspond to 66 percent of the total of 110,000 person-years projected.¹⁴

The active-treatment group had a relative risk of lung cancer of 1.28 (95 percent confidence interval, 1.04 to 1.57; $P=0.02$), as compared with the placebo group (Table 2). This result includes relative risks of 1.40 (95 percent confidence interval, 0.95 to 2.07) for workers exposed to asbestos, 1.42 (95 percent confidence interval, 1.07 to 1.87) for heavy smokers who were smoking at the time of randomization, and 0.80 (95 percent confidence interval, 0.48 to 1.31) for heavy smokers who were no longer smoking at the time of randomization. There was no statistical evidence of heterogeneity of the relative risk among these subgroups. Figure 1 shows the cumulative incidence of lung cancer after randomization; the incidence in the active-treatment and placebo groups was virtually identical for the first 18 months. There was no statistically significant effect of the intervention on

survival after the diagnosis of lung cancer (relative risk of survival after diagnosis of lung cancer in the active-treatment group as compared with the placebo group, 1.05; 95 percent confidence interval, 0.80 to 1.37).

Incidence of Other Cancers

Active treatment had no statistically significant effect on the risk of mesothelioma. There were 23 cases: 14 in the active-treatment group and 9 in the placebo group. The remaining 1030 new cases of cancer (including the 300 prostate cancers, the second most common cancer in this population) were distributed nearly evenly between the two treatment groups.

Mortality Rates

As shown in Table 2 and Figure 2, the mortality rate was 17 percent higher in the active-treatment group than in the placebo group ($P=0.02$). Among the population of heavy smokers, the relative risk was not significantly different between those who were smoking at the time of randomization and those who were no longer smoking at that time (relative risk, 1.15 vs. 1.06).

Analysis according to the cause of death (confirmed causes only; $n=764$) showed that in the active-treatment group, as compared with the placebo group, the relative risk of death from any cause was 1.18 (95 percent confidence interval, 1.02 to 1.37); of death from lung cancer, 1.46 (95 percent confidence interval, 1.07 to 2.00); and of death from cardiovascular causes (codes 390 to 459 and 798 of the *International Classification of Diseases, 9th Revision, Clinical Modification*), 1.26 (95 percent confidence interval, 0.99 to 1.61). As shown in Figure 2, there was no significant difference between treatment groups in the incidence of death from all causes during the first 24 months. A review of all causes of death revealed no additional statistically significant differences between the treatment groups.

DISCUSSION

CARET was initiated in 1983 to test the hypothesis that beta carotene and vitamin A, through complementary antioxidant and differentiation-promoting actions and possibly through immunologic protective effects, could reduce the incidence of lung cancer in high-risk populations. The trial met high standards for accrual, efficiency, quality assurance, and ascertainment of end points. There have been no side effects attributable to the intervention regimen. The participants have shown a high level of commitment to the trial.

The results of the trial are troubling. There was no support for a

Table 1. Risk Factors among the Participants at Base Line.*

CHARACTERISTIC	WORKERS EXPOSED TO ASBESTOS		HEAVY SMOKERS	
	ACTIVE TREATMENT	PLACEBO	ACTIVE TREATMENT	PLACEBO
No. randomized	2044	2016	7376†	6878†
Age — yr	57±7	57±7	58±5	58±5
Female sex — no. (%)	0	0	3208 (43)	3081 (45)
Race or ethnic group — no. (%)				
White	1805 (88)	1775 (88)	7000 (95)	6487 (94)
Black	152 (7)	153 (8)	103 (1)	122 (2)
Hispanic	36 (2)	43 (2)	101 (1)	95 (1)
Other or unknown	51 (2)	45 (2)	172 (2)	174 (3)
Smoking status — no. (%)				
Never smoked	68 (3)	64 (3)	0	0
Former smoker	1195 (58)	1175 (58)	2473 (34)	2331 (34)
Current smoker	781 (38)	777 (39)	4903 (66)	4547 (66)
Cigarettes smoked/day				
Former smokers	25±12	25±12	28±11	28±11
Current smokers	24±10	25±10	24±9	24±8
Pack-years of smoking‡	43±24	42±24	50±21	49±20
Years since quitting smoking§	10±8	10±8	3±2	3±2

*Plus-minus values are means ±SD. Because of rounding, not all columns total 100 percent.
†The imbalance in the numbers is due to the assignment of 3 pilot participants to active treatment for every 1 assigned to placebo (773 to active treatment vs. 256 to placebo).
‡Only former and current smokers were included.
§Only former smokers were included.

Table 2. Incidence and Estimated Relative Risk of Lung Cancer and Death from All Causes.*

GROUP	NO. OF SUBJECTS		UNREFUTED CASES OF LUNG CANCER/1000 PERSON-YR		P VALUE†	LUNG CANCER		DEATHS/1000 PERSON-YR		P VALUE†	DEATH FROM ALL CAUSES	
			ACTIVE TREATMENT	PLACEBO		RELATIVE RISK‡	95% CI	ACTIVE TREATMENT	PLACEBO		RELATIVE RISK‡	95% CI
	ACTIVE TREATMENT	PLACEBO	ACTIVE TREATMENT	PLACEBO		RELATIVE RISK‡	95% CI	ACTIVE TREATMENT	PLACEBO		RELATIVE RISK‡	95% CI
All subjects	9420	8894	5.92	4.62	0.02	1.28	1.04–1.57	14.45	11.91	0.02	1.17	1.03–1.33
Workers exposed to asbestos	2044	2016	6.05	4.33	0.08	1.40	0.95–2.07	17.76	14.30	0.04	1.25	1.01–1.56
Heavy smokers	7376	6878	5.87	4.74	0.09	1.23	0.96–1.56	13.26	10.91	0.14	1.13	0.96–1.32

*CI denotes confidence interval.
†The P values were calculated by two-sided log-rank tests stratified according to the risk group (workers exposed to asbestos or heavy smokers), time of recruitment (pilot study or subsequent period), and study center (six centers).
‡Estimated relative risk in the active-treatment group as compared with the placebo group. The log-rank test, stratified according to risk group, time of recruitment, and study center, was used to estimate the relative risk.

beneficial effect of beta carotene or vitamin A, in spite of the large advantages inferred from observational epidemiologic comparisons of extreme quintiles or quartiles of dietary intake of fruits and vegetables or of dietary intake or serum levels of beta carotene or vitamin A.^{19,20} With 73,135 person-years of follow-up, the active-treatment group had a 28 percent higher incidence of lung cancer than the placebo group, and the overall mortality rate and the rate of death from cardiovascular causes were higher by 17 percent and 26 percent, respectively.

These results confirm and extend the unexpected results reported for beta carotene in the ATBC Cancer Prevention Study in Finland.¹⁰ We cannot distinguish the effects of beta carotene from those of vitamin A, since the two agents were administered in combination, under the hypothesis that they might have a favorable effect through complementary molecular actions.⁹

The second interim analysis led our safety and endpoints monitoring committee and steering committee to recognize the extremely limited prospect of a favorable overall effect, as well as the possibility of true adverse effects. The decision to stop the intervention was made by the steering committee on January 11, 1996. It is possible that the excess mortality in the active-treatment group may have vanished or become statistically insignificant with completion of the intended intervention period plus several years of follow-up; such reversals of findings have occurred both in the course of a single large, randomized trial^{21,22} and in subsequent randomized trials of the same agent or class of agents.^{23–25} However, it was impossible to ignore the results of the ATBC Cancer Prevention Study¹⁰ in deciding whether to stop the active-intervention phase.

We have no explanation for the possible adverse associations that we have observed to date. There was no evidence of systemic toxicity in any organ from the vitamin A or, except for the expected skin yellowing, the beta carotene. The regimen did not produce clinically important hypertriglyceridemia.²⁶ We considered continuing the trial with the retinyl palmitate alone; however, the need to rerandomize, the extended follow-up required, and the uncertainty about the involvement of the vitamin A made this plan infeasible.

In this trial, beta carotene treatment raised the median serum beta carotene levels to 12 times the baseline levels and the placebo group's median values. Such levels may conceivably be toxic or at least cause serious disequilibrium with other compounds important to redox relations or other cellular mechanisms. Beta carotene has been postulated to have a pro-oxidant effect under certain nonphysiologic conditions.^{27,28} One study reported that the administration of beta carotene drastically lowered vitamin E levels,²⁹ but we³⁰ and three other groups^{10,31,32} have found no such effect. In preliminary analyses of serum beta carotene levels during active treatment, we could find no support for the hypothesis that subjects with the highest serum levels of beta carotene were at greater risk for lung cancer or death from cardiovascular causes, cancer, or any cause.

The results of our study and the ATBC Cancer Prevention Study¹⁰ in populations at high risk for lung cancer and cardiovascular disease and the finding of the Physicians' Health Study¹¹ of no benefit or harm after 12 years of beta carotene treatment clearly do not support

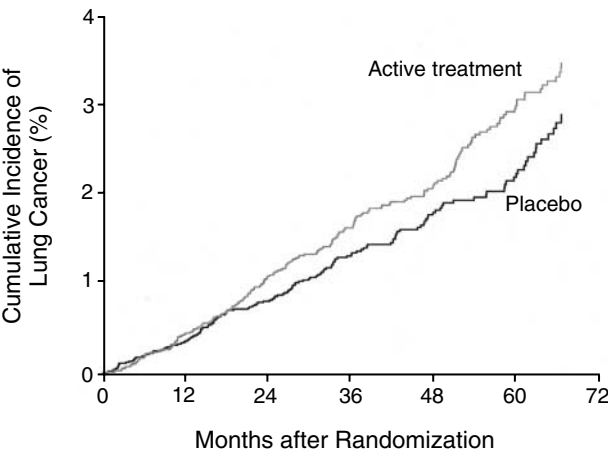


Figure 1. Kaplan-Meier Curves of the Cumulative Incidence of Lung Cancer among Participants Receiving Active Treatment and Those Receiving Placebo.
Data are shown only through 5½ years of follow-up because of the small numbers of participants beyond that time.

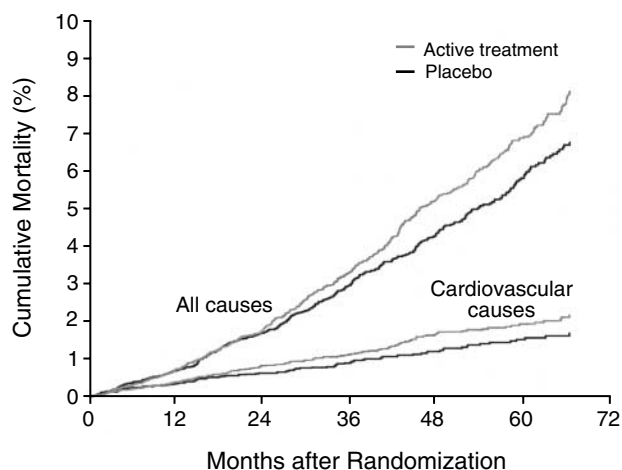


Figure 2. Kaplan-Meier Curves of the Cumulative Incidence of Death from All Causes and Confirmed Cardiovascular Causes among Participants Receiving Active Treatment and Those Receiving Placebo.

Data are shown only through 5½ years of follow-up because of the small numbers of participants beyond that time.

the widely accepted conclusion drawn from observational epidemiologic studies that beta carotene is a primary component responsible for the association of lower risks of cancer and death from cardiovascular causes with high intakes of fruits and vegetables.^{19,33} Such studies typically compare extreme subgroups for such dietary features, ignoring or only crudely adjusting for many other potentially relevant variables, such as the intake of red meat, physical activity, life situations, and other behavior.²⁰ The dietary associations seemed well matched to serum beta carotene measurements; as in other observational analyses, in our study base-line serum beta carotene levels were inversely correlated with the subsequent incidence of lung cancer in both groups. However, randomized prevention trials are needed to test the hypothesis that increased beta carotene intake can be protective.

The results of four large-scale chemoprevention trials of beta carotene and related agents can be summarized. The ATBC Cancer Prevention Study¹⁰ tested daily supplementation with 20 mg of beta carotene and 50 mg of alpha-tocopherol (two-by-two factorial design) in 29,133 male smokers. The Physicians' Health Study¹¹ tested supplementation with 50 mg of beta carotene on alternate days in 22,071 male physicians, 50 percent of whom had never smoked, 39 percent of whom were former smokers, and 11 percent of whom were currently smoking. We tested daily supplementation with a combination of 30 mg of beta carotene and 25,000 IU of retinyl palmitate. Finally, a study conducted in Linxian, China,³⁴ assessed the value of daily supplementation with a combination of 15 mg of beta carotene, 50 µg of selenium, and 30 mg of alpha-tocopherol as compared with three other combinations of vitamins and minerals in a complex factorial design in 29,584 adults presumed

to be vitamin- and mineral-deficient — a very different population from those examined in the other studies. In the ATBC Cancer Prevention Study, 876 new cases of lung cancer were diagnosed, yielding a relative risk of lung cancer of 1.18 among subjects who received beta carotene (with or without alpha-tocopherol), as compared with those who did not. In the Physicians' Health Study, 170 new cases of lung cancer were diagnosed, for a relative risk of lung cancer of 0.93 among men taking beta carotene, as compared with those who received placebo. In our study, there were 388 new cases of lung cancer, yielding a relative risk of such cancer of 1.28 among the subjects who received beta carotene and retinyl palmitate, as compared with those who received placebo. The Linxian study did not report the incidence of lung cancer. Among the subjects who received beta carotene, the relative risk of death from any cause was 1.08 in the ATBC Cancer Prevention Study (3570 deaths), 1.01 in the Physicians' Health Study (1947 deaths), 1.17 in our trial (974 deaths), and 0.91 in the Linxian study (2127 deaths).

Reversing or overcoming lifelong metabolic or exogenous risk factors may require 5 to 10 years or more to account for the latent periods of cancers. Favorable effects may be particularly difficult to achieve in the face of a continuing carcinogenic and atherogenic assault in smokers; alternatively, antioxidants and antiproliferative agents might act on the constituents of cigarette smoke. Long-term follow-up both during and after active treatment with potential chemopreventive agents is essential if we are to have any hope of observing long-term benefits and evaluating long-term risks. During the postintervention follow-up of our study subjects, as end points continue to accrue, we will conduct laboratory analyses and analyze various subgroups, particularly former smokers.

Our findings provide important new information with respect to public policy and public health. When these results are combined with those from the ATBC Cancer Prevention Study¹⁰ and the Physicians' Health Study,¹¹ they make it clear that there can be little enthusiasm about the efficacy or safety of supplemental beta carotene or vitamin A in efforts to reduce the burdens of cancer or heart disease in certain populations. However, we still recommend the dietary intake of fruits and vegetables.

Other agents that prevent lung cancer and coronary heart disease must be identified and subjected to rigorous trials of safety and efficacy. Meanwhile, to reduce the risk of these diseases we must rely primarily on three approaches: smoking cessation, prevention of smoking, and avoidance of occupational and environmental exposure to carcinogenic substances.

We are indebted to the study subjects, staff members, and investigators; to the members of the safety and end-points monitoring committee over the past several years (Anthony Miller, Robert Bruce, Julie Buring, Frank Iber, and O. Dale Williams); and to our colleagues who provided data from the Physicians' Health Study.

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