α-Tocopherol and β-Carotene Supplements and Lung Cancer Incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: Effects of Base-line Characteristics and Study Compliance

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Background: **Experimental and epidemiologic investigations suggest that α-tocopherol (the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts, and other foods) and β-carotene (a plant pigment and major precursor of vitamin A found in many yellow, orange, and dark-green, leafy vegetables and some fruit) might reduce the risk of cancer, particularly lung cancer. The initial findings of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) indicated, however, that lung cancer incidence was increased among participants who received β-carotene as a supplement. Similar results were recently reported by the Beta-Carotene and Retinol Efficacy Trial (CARET), which tested a combination of β-carotene and vitamin A. *Purpose:* We examined the effects of α-tocopherol and β-carotene supplementation on the incidence of lung cancer across subgroups of participants in the ATBC Study defined by base-line characteristics (e.g., age, number of cigarettes smoked, dietary or serum vitamin status, and alcohol consumption), by study compliance, and in relation to clinical factors, such as disease stage and histologic type. Our primary purpose was to determine whether the pattern of intervention effects across subgroups could facilitate further interpretation of the main ATBC Study results and shed light on potential mechanisms of action and relevance to other populations. *Methods:* A total of 29 133 men aged 50-69 years who smoked five or more cigarettes daily were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), α-tocopherol and β-carotene, or a placebo daily for 5-8 years (median, 6.1 years). Data regarding smoking and other risk factors for lung cancer and dietary factors were obtained at study entry, along with measurements of serum levels of α-tocopherol and β-carotene. Incident cases of lung cancer (n = 894) were identified through the Finnish Cancer Registry and death certificates. Each lung cancer diagnosis was independently confirmed, and histology or cytology was available for 94% of the cases. Intervention effects were evaluated by use of survival analysis and proportional hazards models. All *P* values were derived from two-sided statistical tests. *Results:* No overall effect was observed for lung cancer from α-tocopherol supplementation (relative risk [RR] = 0.99; 95% confidence interval [CI] = 0.87-1.13; *P* = .86, logrank test). β-Carotene supplementation was associated with increased lung cancer risk (RR = 1.16; 95% CI = 1.02-1.33; *P* = .02, logrank test). The β-carotene effect appeared stronger, but not substantially different, in participants who smoked at least 20 cigarettes daily (RR = 1.25; 95% CI = 1.07-1.46) compared with those who smoked five to 19 cigarettes daily (RR = 0.97; 95% CI = 0.76-1.23) and in those with a higher alcohol intake (≥11 g of ethanol/day [just under one drink per day]; RR = 1.35; 95% CI = 1.01-1.81) compared with those with a lower intake (RR = 1.03; 95% CI = 0.85-1.24). *Conclusions:* Supplementation with α-tocopherol or β-carotene does not prevent lung cancer in older men who smoke. β-Carotene supplementation at pharmacologic levels may modestly increase lung cancer incidence in cigarette smokers, and this effect may be associated with heavier smoking and higher alcohol intake. *Implications:* While the most direct way to reduce lung cancer risk is not to smoke tobacco, smokers should avoid high-dose β-carotene supplementation. [J Natl Cancer Inst 1996;88:1560-70]**

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, or ATBC Study, a large, double-blinded, placebo-controlled intervention trial, tested whether the use of α-tocopherol

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or β-carotene supplements prevents the occurrence of lung cancer (*1*). α-Tocopherol is the most prevalent chemical form of vitamin E that occurs naturally in vegetable oils, seeds, grains, nuts, and other foods, and β-carotene is a plant pigment and major precursor of vitamin A found in many yellow, orange, and dark-green, leafy vegetables and some yellow fruit. The initial cancer- and mortality-related findings of the ATBC Study have been reported (*2,3*) and indicated no reduction in the incidence of or mortality from lung cancer among participants who received either α-tocopherol or β-carotene as a supplement. Instead, an increase in incidence was observed among participants who received β-carotene (20 mg daily). A similar result for β-carotene was recently reported by the Beta-Carotene and Retinol Efficacy Trial (CARET), which halted its daily intervention of β-carotene (30 mg) combined with retinyl palmitate (25 000 IU) following observation of increased incidence of and total mortality from lung cancer (*4*). At the same time, these findings remain contrary to nearly all previous epidemiologic and laboratory evidence suggesting a beneficial relationship between carotenoids, particularly β-carotene, and lung cancer risk (*5-9*).

We report here the final lung cancer results from the ATBC Study, utilizing all cases identified during the intervention. We examined the effects of α-tocopherol and β-carotene supplementation on the incidence of lung cancer across subgroups of participants defined by base-line characteristics (e.g., age, number of cigarettes smoked, dietary or serum vitamin status, and alcohol consumption), by study compliance, and in relation to clinical factors, such as disease stage and histologic type. Our primary purpose was to determine whether the pattern of intervention effects across subgroups could facilitate further interpretation of the main ATBC Study results and shed light on the questions of causality, potential mechanisms of action, and relevance to other populations.

Subjects and Methods

Background and Base Line

Details concerning study rationale, methods, participant characteristics, and compliance have been reported (*1*). In brief, 29 133 male smokers (smokers of five or more cigarettes daily at study entry) 50-69 years old were randomly assigned within each of the 14 study centers to receive α-tocopherol (50 mg, as *dl*-α-tocopheryl acetate), β-carotene (20 mg), α-tocopherol plus β-carotene, or placebo daily for 5-8 years (median, 6.1 years) in a double-blinded fashion. The 2 × 2 factorial design allowed assessment of the two intervention agents independently, with nearly one half of the participants (n = 14 564) receiving α-tocopherol and the other one half (n = 14 569) not receiving the agent; similarly, approximately half (n = 14 560) received β-carotene and approximately half (n = 14 573) did not. We excluded men with a previous cancer or with another serious illness, men who used vitamin E, vitamin A, or β-carotene supplements in excess of predefined doses or anticoagulants, or men who had lung cancer detected on a pre-randomization chest film. The ATBC Study was approved by the institutional review boards of both the National Public Health Institute of Finland and the U.S. National Cancer Institute, and written informed consent was obtained from each participant prior to randomization.

Medical, dietary, smoking, occupational asbestos exposure, and other background data were obtained at study entry, along with height and weight, a chest film, and serum samples. Dietary intakes of vitamins E and C, β-carotene and other carotenoids, and alcohol were estimated from a diet history questionnaire (10) and were available for 27 111 participants (93%). Serum concentrations of α-tocopherol, β-carotene, and retinol were determined by high-performance liquid chromatography (11) in one laboratory that participated in the National Institute of Standards and Technology (then National Bureau of Standards) serum micronutrient quality-assurance program. The between-run coefficients of variation were 2.2% for α-tocopherol, 3.6% for β-carotene, and 2.4% for retinol.

Follow-up

Participants had three follow-up visits annually, during which medical (illnesses and symptoms), smoking, and compliance data were collected. A mid-study serum sample was obtained after 3 years of supplementation. Capsule compliance while on the study was high (median = 99% of on-study pills taken). Persistent skin yellowing, defined as being self-reported at two thirds or more of the follow-up visits, was present in 8.8% of the men in the β-carotene arm versus only 0.3% of those not taking β-carotene. A study chest film was obtained every 2⅓ years and at study exit. The film was read by radiologists or pulmonary physicians at the hospital associated with the respective study centers. The chest film at study exit was available for all but 494 surviving men, yielding a 98% success rate that was equal across the supplementation groups.

Case Ascertainment and Review

Lung cancers were identified through the Finnish Cancer Registry and death certificates. All men with incident lung cancer diagnosed while on the trial (through April 30, 1993) are included in this article (n = 894). An additional 18 cases were identified after the initial report was published (*2*); most of these cases were detected from the study chest films taken just prior to trial closure, but their final clinical diagnostic work-ups and central clinical and pathology reviews were not completed until recently. Three men had two separate lung cancers diagnosed, of which only the first diagnosed lung cancer was considered for analysis. Six cases of carcinoma in situ were identified but were excluded from analysis (no difference by supplementation group). The Clinical Review Committee reviewed medical records to confirm and stage each case according to the criteria of the American Joint Committee on Cancer (*12*). A randomly selected sample of cases (n = 105) was re-reviewed by an independent lung oncologist; in all cases, the diagnosis of primary lung cancer was confirmed. Cases with available histology (76%) were also reviewed by two pathologists, and those with cytology only (18%) were reviewed by two pulmonary cytologists. The International Classification of Diseases for Oncology (ICD-O) was used (*13*). Clinical data alone were available for 6%. End-point ascertainment and review were performed blinded to intervention allocation.

Deaths were identified through the Central Population Registry, and a study physician reviewed the underlying cause of death. Only deaths having lung cancer as the underlying cause [ICD-9 (*14*) code 162] were included in analyses of lung cancer survival and mortality.

An independent Data and Safety Monitoring Board convened twice annually to monitor trial progress and to study unblinded data that were relevant to intervention safety and efficacy.

Statistical Analysis

In all analyses (except where indicated), the subjects were allocated to the intervention arm as randomized; i.e., the intention-to-treat principle was used. Follow-up time was accumulated until the date of lung cancer diagnosis or the date of death or April 30, 1993, whichever came first. Cases of cancer other than lung cancer were ignored in the analyses. Kaplan–Meier cumulative incidence curves were estimated for the four intervention groups, along with two-sided nominal *P* values derived from the unweighted logrank statistic (*15*). The trial intervention effect was assessed by use of proportional hazards regression models (*15*), and time since randomization was modeled nonparametrically. In spite of nearly perfect base-line risk factor balance between intervention groups in the whole study population, simultaneous adjustment was made for base-line age, number of cigarettes smoked daily, years of cigarette smoking, and body mass index (i.e., kg/m^2) (as continuous variables), each being significantly associated with lung cancer risk. The adjusted relative risk (RR) of lung cancer incidence and its 95% confidence interval (CI) are reported. The interaction between the intervention effects of α-tocopherol and β-carotene was tested by including a cross-product term in the model. To evaluate whether there were biases related to detection or diagnosis of lung cancer, we conducted separate analyses that were restricted to cases diagnosed on the basis of a study chest film screening, cases having pathologic confirmation, and participants not reporting yellowing of the skin while on the study. A separate analysis was also conducted in which a regression model was used that allowed participants' status regarding persistent self-

reported skin yellowing to change over time. Subgroup-specific lung cancer incidence rates were also calculated, standardized to the age and smoking (i.e., cigarette) distributions of the entire cohort.

Effect modification by base-line factors was assessed through subgroup analysis, with interaction or trend being tested as the relevant cross-product term (e.g., intervention group × the factor as a scored variable) included in the hazards model. Chi-squared tests for frequency tables were used to compare the distributions of cases according to method of detection, disease stage, and histology in the intervention groups. To evaluate the relation between intervention effects and time, we analyzed lung cancer RR by length of follow-up, including in the hazards model a cross-product term for intervention group × time since randomization. We also assessed whether lung cancer incidence was influenced by duration of active intervention determined by study compliance—not an intention-to-treat analysis. For this assessment, subjects were divided into three categories: 1) those who stopped taking their allocated capsules (i.e., stopped participating) during the 1st year, 2) those who stopped participating during years 1-3, and 3) the remaining men who continued attendance for more than 3 years. Within each subgroup, we calculated an RR for α-tocopherol versus no α-tocopherol and β-carotene versus no β-carotene from the proportional hazards model. To reduce the possible influence of lung cancer having caused the subjects in groups 1 and 2 to become noncompliant, we examined only the RRs from the 4th year of follow-up onward. All *P* values were derived from two-sided tests.

Results

Participant Characteristics

We have previously reported that randomization yielded intervention groups balanced at base line for factors related to lung cancer risk (*1*,*2*). For all intervention groups, median age at study entry was 57 years, number of cigarettes smoked daily was 20, and duration of smoking prior to study entry was 36 years. Capsule compliance, number of cigarettes smoked per day, smoking cessation, and dietary intake of β-carotene, vitamin E, and vitamin C were also identical across the intervention groups during the study. For example, more than 6100 (22%) participants reported having stopped smoking at some point during the 5- to 8-year trial, with less than a one percentage point difference in the cessation rate across groups.

Lung Cancer Incidence and Mortality

By the end of the study, 894 men with incident lung cancer were identified: 204 in the α-tocopherol-alone group, 242 in the β-carotene-alone group, 240 in the group given α-tocopherol plus β-carotene, and 208 in the placebo group. Cumulative incidence of lung cancer for each of the four intervention groups is shown in Fig. 1. The curves for each of the two groups who received β-carotene lay above those of the non-β-carotene groups (P = .02, logrank test for β-carotene versus no β-carotene), whereas the curve for the α-tocopherol-alone group closely followed that for the placebo group. The logrank test was not statistically significant for either the four group comparison (P = .11) or for α-tocopherol versus no α-tocopherol (P = .86), and the two agents did not interact (P = .79).

From the multivariate proportional hazards model, the RR for lung cancer incidence for α-tocopherol supplementation was 0.99 (95% CI = 0.87-1.13); for β-carotene, it was 1.16 (95% CI = 1.02-1.33). More lung cancers (10 versus four) occurred in the β-carotene arm in the majority of study centers. Results obtained for histologically or cytologically confirmed cancers (n = 840) were equivalent to those obtained for all cases combined, with the RR (95% CI) for α-tocopherol being 1.00 (0.87-1.14) and for β-carotene being 1.15 (1.00-1.31). The presence (or absence) of persistent skin yellowing also did not materially influence the β-carotene effect. When the effect of α-tocopherol was examined by follow-up year since randomization, there was a decline in RR from 1.29 (95% CI = 0.81-2.06) during year 1 to 0.85 (95% CI = 0.58-1.25) during years 7 and 8 combined (P for trend = .13) (Fig. 2, A). The RR of lung cancer for β-carotene

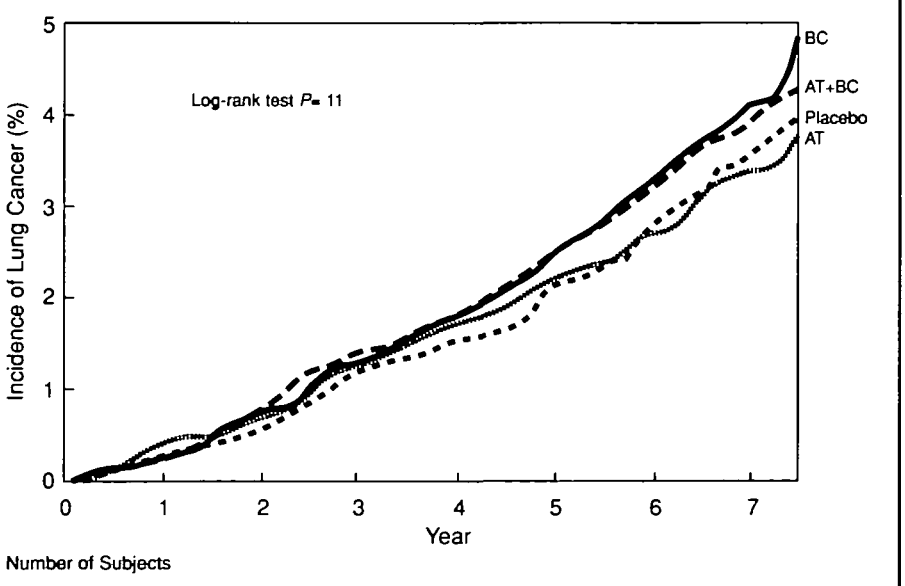

Fig. 1. Cumulative incidence of lung cancer according to intervention allocation. Logrank test for comparison of α-tocopherol (AT) to no α-tocopherol (P = .86) and for comparison of β-carotene (BC) to no β-carotene, P = .02.

supplementation fluctuated during the first years but ranged from 1.15 to 1.36 from the 4th follow-up year onward (P for trend = .24) (Fig. 2, B).

Lung cancer deaths numbered 553: 125 in the α-tocopherol-alone group, 140 in the β-carotene-alone group, 154 in the group given α-tocopherol plus β-carotene, and 134 in the placebo group. The cumulative mortality curves closely paralleled the curves for incidence, and the logrank test for mortality yielded P = .82 for α-tocopherol versus no α-tocopherol and P = .11 for β-carotene versus no β-carotene. No differences in lung cancer survival time were observed among the study arms. Also, the Kaplan–Meier survival curves were identical for all supplementation groups (data not shown).

Clinical Characteristics

The distibutions of cases according to method of detection (i.e., through periodic study chest films compared with measures initiated by symptoms or non-study health screenings), disease stage, and histology were generally similar among the α-tocopherol- or β-carotene-supplemented participants compared

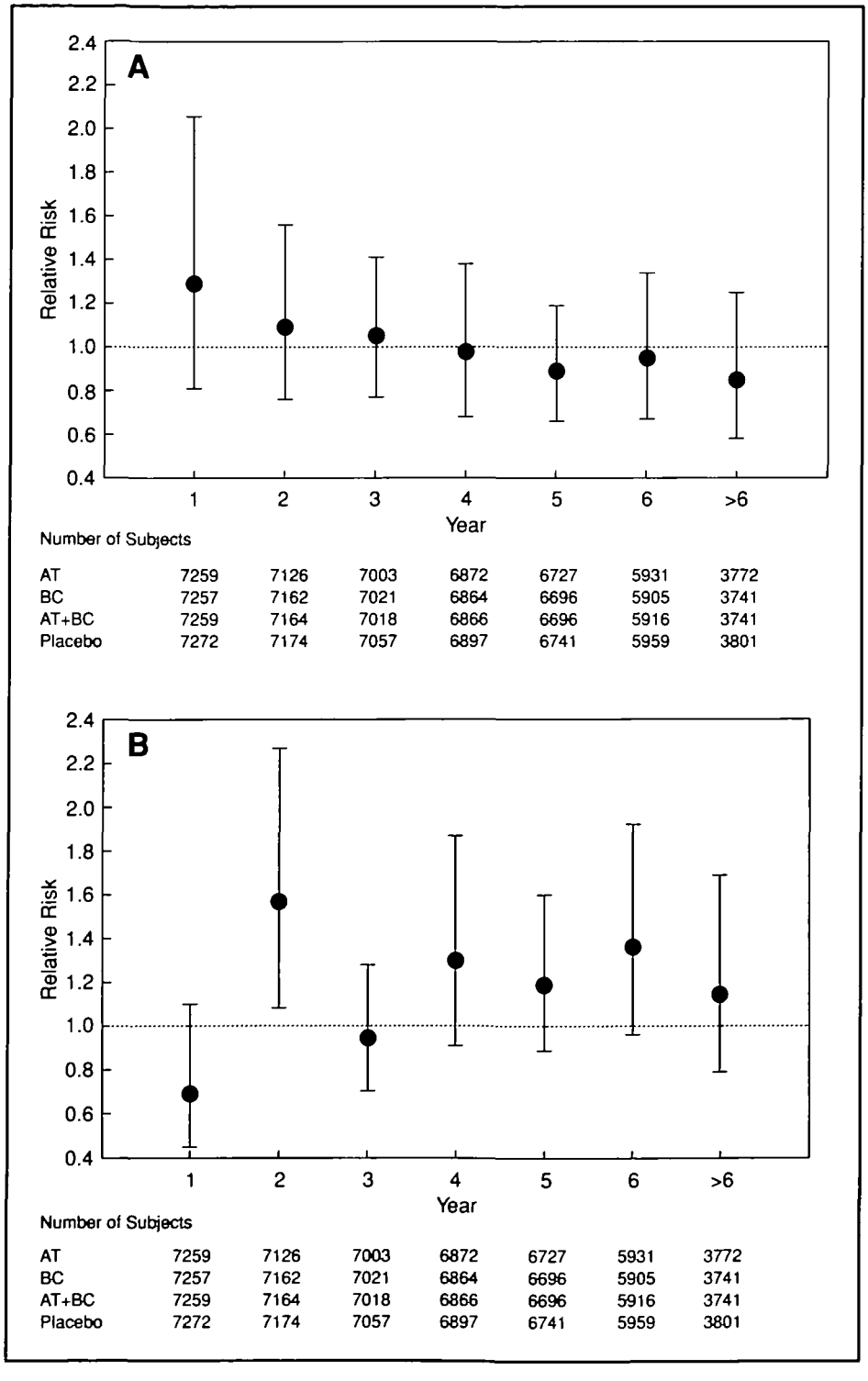

Fig. 2. Relative risk of lung cancer by follow-up year since randomization among men who received α-tocopherol (AT) compared with men who did not (**A**) and among men who received β-carotene (BC) compared with men who did not (**B**). Calculated from period-specific proportional hazards models that included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as a continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group.

with participants in the respective nonsupplemented group (Table 1). Overall, 21% of the cases were diagnosed in stage 1, 14% in stage 2, and 35% and 30% in stages 3 and 4, respectively, and this distribution did not differ significantly by intervention allocation (chi-squared test [3 *df*], 6.87 (P = .08) for α-tocopherol and 0.88 [P = .83] for β-carotene). The major histologic types were represented proportionally among the intervention arms (chi-squared test, P = .79 for α-tocopherol and P = .90 for β-carotene); however, large- or giant-cell cancers, included within the "other" category, showed a somewhat greater excess in the β-carotene group (26 cases versus 15 cases).

Modifying Effects of Lung Cancer Risk Factors

Tables 2 and 3 show stratum-specific lung cancer incidence rates and the estimated effects of α-tocopherol and β-carotene supplementation within subgroups of several lung cancer risk factors at base line. Incidence rates generally increased with age, number of cigarettes smoked daily, years of cigarette smoking, degree of inhalation, and occupational asbestos exposure, which is in agreement with known etiologic associations.

No statistically significant modification of the intervention effect was observed for these factors (Tables 2 and 3), although the RR for β-carotene supplementation was somewhat elevated among smokers of at least 20 cigarettes daily (RR = 1.25; 95% CI = 1.07-1.46) compared with smokers of five to 19 cigarettes daily (RR = 0.97; 95% CI = 0.76-1.23). Smoking cessation during the study, while related to lower lung cancer incidence, did not materially alter the effects of either intervention (data not shown).

Modifying Effects of Vitamin and Alcohol Intake and Serum Vitamin Concentrations

Consistent with most previous epidemiologic studies, there was a trend toward lower lung cancer incidence among persons with higher base-line vitamin intake or serum concentrations (Tables 4 and 5). Similar associations were seen in the placebo group. Modification of the α-tocopherol and β-carotene supplementation effects by these dietary and serum factors was limited (Tables 4 and 5). A declining trend in the RR of lung cancer was suggested for β-carotene intervention with increasing dietary vitamin E intake (P for trend = .03) (Table 5). Such an interaction was not observed, however, for the quartiles of serum α-tocopherol.

The effect of β-carotene supplementation increased marginally as alcohol consumption increased (P for trend = .08 for alcohol modeled as scored quartiles; P = .05 for alcohol as a continuous variable). Among men who drank at least 11 g of ethanol daily (i.e., one alcoholic drink or more per day, the median for the cohort), the β-carotene intervention RR was 1.35 (95% CI = 1.01-1.81), whereas among those with intake less than the median, RR was 1.03 (95% CI = 0.85-1.24). This pattern was suggested for each alcoholic beverage type (i.e., beer, spirits, and wine). Nondrinkers, who made up only 11% of the study population, also showed a reduced β-carotene effect (RR = 0.93; 95% CI = 0.65-1.33). The β-carotene–alcohol interaction did not differ by smoking level.

Base-line dietary intake of fat, fiber, fruit, vegetables, carotenoids, and tocopherols and serum and dietary cholesterol did not modify the effects of the trial supplements (data not shown). Also, neither body weight nor body mass index was significantly related to the intervention effect of either agent, although the lung cancer RR for the α-tocopherol intervention group was lowest among men of lower body weight (i.e., men who would, other factors being equal, have a higher effective dose on an mg/kg basis) and increased with body weight.

Duration of Intervention and Capsule Compliance

We examined the effect of duration of intervention on the relative incidence of lung cancer during the later part of the study (i.e., >3 years) by comparing the intervention effects among subjects who had taken study capsules for different periods of time (Table 6). For α-tocopherol supplementation, the duration of active intervention had little effect on lung cancer incidence. For β-carotene supplementation, an increase in RR was seen among the participants who had been taking study capsules for more than 1 year, although the trend was not statistically significant (P = .23). While these analyses are subject to

Table 1. Number of lung cancer cases by α-tocopherol and β-carotene intervention assignment and detection method, stage, and histology*

	No. of cases			
	α-Tocopherol	No α-tocopherol	β-Carotene	No β-carotene
All cases	444	450	482	412
Clinical factor and category				
Detection method				
Periodic study chest film	110	113	118	105
Other	334	337	364	307
Stage at diagnosis				
1	94	92	98	88
2	48	75	70	53
3	161	150	171	140
4	140	128	141	127
Histologic type				
Squamous cell carcinoma	193	196	214	175
Small-cell carcinoma	109	108	113	104
Adenocarcinoma	77	68	75	70
Other histologies combined	50	60	61	49

*Number of cases within intervention arm and factor reflect those with available data and may not equal the total.

Table 2. Number of cases, age- and cigarette-adjusted incidence rate (per 10^5 person-years), and relative risk from proportional hazards models for lung cancer by α-tocopherol intervention and level of base-line lung cancer risk factors*

	α-Tocopherol		No α-tocopherol		
	No. of cases	Rate	No. of cases	Rate	RR (95% CI)†
Total	444	532	450	545	0.99 (0.87-1.13)
Factor and category					
Age, y‡					
50-54	68	223	64	207	1.05 (0.74-1.48)
55-59	147	538	121	439	1.25 (0.98-1.59)
60-64	147	795	172	967	0.81 (0.65-1.01)
65-69	82	1024	93	1126	0.92 (0.69-1.24)
					P for trend = .21
Cigarettes/day‡					
5-19	125	411	132	430	0.98 (0.76-1.25)
20-29	210	543	230	591	0.92 (0.76-1.11)
≥30	109	713	88	592	1.18 (0.89-1.57)
					P for trend = .48
Years of cigarette smoking					
≤30	44	358	27	211	1.57 (0.98-2.54)
31-35	56	362	49	405	1.16 (0.79-1.70)
36-41	131	534	144	601	0.93 (0.73-1.18)
>41	212	865	229	1200	0.92 (0.76-1.10)
					P for trend = .23
Cigarette smoke inhalation					
Never/seldom	27	371	30	412	0.94 (0.56-1.58)
Often	170	566	157	519	1.08 (0.87-1.34)
Always	247	547	262	592	0.94 (0.79-1.12)
					P for trend = .62
Occupational asbestos exposure					
Yes	10	633	11	640	0.98 (0.41-2.32)
No	434	530	439	543	0.99 (0.86-1.13)
					P for interaction = .97

*Proportional hazards models were conducted within each subgroup and included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as a continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group. Interaction between intervention (yes, no) and each factor (scored categories) was tested by a separate cross-products term. Number of cases within intervention arm and factor reflect those with available data and may not equal the total.

†Relative risk (95% confidence interval). Two-sided *P* values.

‡Crude rates are presented for strata of age and cigarettes per day.

self-selection bias, they seem to suggest that the longer the supplementation, the more harmful the β-carotene effect.

Capsule compliance varied in a very narrow range among the participants, and it improved with time. Compliance was not significantly related to the effect of either intervention agent. There was, however, a slight tendency for lung cancer risk to increase with the proportion of β-carotene capsules taken: RRs (95% CIs) were 1.05 (0.83-1.33), 1.15 (0.94-1.40), and 1.32 (1.00-1.73) for the categories less than 95%, 95%-99%, and 100%.

Serum Response in the β-Carotene Group

In a separate analysis restricted to the β-carotene group, we examined whether lung cancer incidence was related to serum β-carotene response to supplementation. Dividing the β-carotene group into tertiles of change in serum β-carotene concentrations after 3 years on the study (tertile cuts in μg/L increase: <2060, 2060-3467, and ≥3468), we found no association between serum response and lung cancer incidence after 3 years. RRs (95% CIs) by increasing tertile were 1.00 (referent), 0.96 (0.71-1.29), and 0.92 (0.68-1.23) (*P* for trend = .56), based on 267 lung cancer cases. Analysis of the absolute on-study serum β-carotene concentrations gave similar results. For tertiles of less than 2262 μg/L, 2262-3715 μg/L, and 3716 μg/L or more, RRs were 1.00, 0.96, and 0.88 (*P* for trend = .40). These analyses are not based on intention to treat, however, and require cautious interpretation. (A separate analysis of lung cancer incidence and serum response to α-tocopherol supplementation gave similar results.)

Discussion

In this randomized, double-blinded, placebo-controlled trial of male cigarette smokers, participants receiving α-tocopherol supplementation showed no change in lung cancer incidence overall but perhaps somewhat lower lung cancer rates relative to those of the non-α-tocopherol group in the later years of follow-up. We observed a 16% excess in incident lung cancers among participants who received β-carotene supplements for an average of 6 years (range, 5-8 years). The β-carotene effect appeared stronger in men with higher alcohol intake (≥11 g ethanol/day) and may have been restricted to those smoking at least 20 cigarettes daily. These findings emerged from multiple comparisons, however, and neither interaction achieved statistical significance.

Results from one (*4*) of two other recently reported large controlled trials of β-carotene supplementation (*4,16*) are similar to our findings. CARET studied 18 314 men and women, among whom 388 lung cancers developed, and observed a 28% increase in lung cancer incidence in participants who received β-carotene (30 mg) and retinyl palmitate (25 000 IU) daily for an

Table 3. Number of cases, age- and cigarette-adjusted incidence rates (per 10^5 person-years), and relative risk from proportional hazards models for lung cancer by β-carotene intervention and level of base-line lung cancer risk factors*

	β-Carotene		No β-carotene		
	No. of cases	Rate	No. of cases	Rate	RR (95% CI)†
Total	482	580	412	497	1.16 (1.02-1.33)
Factor and category					
Age, y‡					
50-54	75	249	57	182	1.34 (0.95-1.90)
55-59	142	515	126	462	1.11 (0.87-1.41)
60-64	163	890	156	868	1.03 (0.82-1.28)
65-69	102	1241	73	907	1.39 (1.03-1.88)
					P for trend = 72
Cigarettes/day‡					
5-19	127	410	130	431	0.97 (0.76-1.23)
20-29	244	635	196	500	1.25 (1.04-1.51)
≥30	111	746	86	563	1.28 (0.97-1.70)
					P for trend = .15
Years of cigarette smoking					
≤30	40	349	31	222	1.28 (0.80-2.05)
31-35	61	560	44	294	1.44 (0.98-2.12)
36-41	142	579	133	554	1.06 (0.84-1.34)
>41	237	1017	204	884	1.15 (0.96-1.39)
					P for trend = .78
Cigarette smoke inhalation					
Never/seldom	30	415	27	368	1.10 (0.66-1.86)
Often	167	565	160	518	1.08 (0.87-1.34)
Always	285	629	224	510	1.23 (1.04-1.47)
					P for trend = .42
Occupational exposure to asbestos					
Yes	10	655	11	677	0.79 (0.33-1.88)
No	472	580	401	493	1.17 (1.03-1.34)
					P for interaction = .38

*Proportional hazards models were conducted within each subgroup and included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as a continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group. Interaction between intervention (yes, no) and each factor (scored categories) was tested by a separate cross-products term. Number of cases within intervention arm and factor reflect those with available data and may not equal the total.

†Relative risk (95% confidence interval). Two-sided *P* values.

‡Crude rates are presented for strata of age and cigarettes per day.

average of 4 years compared with the lung cancer incidence in participants who received placebo (*4*). This trial, composed of both current (60%) and former (39%) heavy smokers, including asbestos-exposed smokers (22%), also found increased total mortality (17%) in the β-carotene plus retinyl palmitate intervention group. Data from the 12-year Physicians' Health Study, on the other hand, showed no material differences in lung cancer incidence between the β-carotene (50 mg every other day) and placebo groups (82 cases in β-carotene group versus 88 taking placebo, crude RR = 0.93) in its all-male, primarily never-smoker (50%) and former-smoker (39%) population (*16*). There were also no differences between the groups in total cancer incidence (RR = 0.98) or in total mortality (RR = 1.01). Other large primary prevention trials of cancer and β-carotene reported to date have not been lung cancer trials or have used β-carotene combined with other agents. The general population trial in Linxian, China, investigated the prevention of esophageal cancer and the lowering of total mortality. It is the only large population trial to demonstrate efficacy for β-carotene supplementation (15 mg daily), but the group who benefited received β-carotene combined with α-tocopherol and selenium, thereby precluding identification of any single efficacious agent (*17*). Only 31 lung cancer deaths were reported among the 792 total cancer deaths in this trial, with slightly fewer (11 versus 20) in the group who received β-carotene, α-tocopherol, and selenium (*18*). No clear benefit for cancer was seen in a companion trial in Linxian that tested daily supplementation with a multiple vitamin–multiple mineral preparation that included β-carotene (15 mg) among persons with esophageal dysplasia (*19*). Other, smaller trials that tested β-carotene separately showed no effect on nonmelanoma skin cancer (*20*), colorectal adenoma (*21,22*), or total cancer mortality (*23*); in combination with retinol, β-carotene had no impact on sputum atypia (*24*). Taken together, the results from these trials suggest it is highly unlikely that supplementation with such pharmacologic doses of β-carotene for several years is beneficial in the prevention of major cancers, and they provide evidence for a disadvantage in cigarette smokers.

The primary objective of this analysis was to determine whether the pattern of β-carotene intervention effects across subgroups could facilitate further interpretation of the main result. While the most powerful single piece of evidence supporting a real effect of β-carotene on lung cancer incidence is the confirmation of our finding in a second large, randomized trial, several aspects of the present data also support this. First, we observed an increase in total mortality, including deaths from non-cancer causes, in the β-carotene group (*2*). Second, while we observed a lung cancer excess in the β-carotene group for nearly all subgroups evaluated, the effect appeared stronger among those who smoked more heavily, a finding consistent

Table 4. Number of cases, age- and cigarette-adjusted incidence rate (per 10^5 person-years), and relative risk from proportional hazards models for lung cancer by α-tocopherol intervention and level of base-line dietary intake (daily) and serum vitamins*

	α-Tocopherol		No α-tocopherol		
	No. of cases	Rate	No. of cases	Rate	RR (95% CI)†
Total	444	532	450	545	0.99 (0.87-1.13)
Dietary factor and category					
Vitamin E, mg					
<8.10	125	614	145	691	0.88 (0.69-1.11)
8.10-10.6	106	537	93	481	1.16 (0.87-1.53)
10.7-14.5	99	521	87	485	1.08 (0.81-1.44)
>14.5	82	464	84	468	0.98 (0.72-1.33)
					P for trend = .49
β-Carotene, mg					
<1.09	113	544	118	593	0.95 (0.73-1.23)
1.09-1.70	109	563	96	488	1.14 (0.87-1.50)
1.71-2.70	102	540	98	518	1.05 (0.80-1.39)
>2.70	88	487	97	520	0.88 (0.66-1.18)
					P for trend = .73
Carotenoids, mg					
<2.79	125	602	129	630	0.98 (0.76-1.25)
2.79-3.91	106	550	98	516	1.08 (0.82-1.42)
3.92-5.52	101	535	99	513	1.06 (0.80-1.40)
>5.52	80	447	83	463	0.91 (0.67-1.24)
					P for trend = .88
Vitamin C, mg					
<70.5	125	606	141	662	0.91 (0.72-1.16)
70.5-97.1	116	583	108	564	1.05 (0.81-1.36)
97.2-131.1	80	427	91	483	0.88 (0.65-1.19)
>131.1	91	519	69	406	1.29 (0.95-1.77)
					P for trend = .18
Retinol, μg					
<809.5	116	582	113	566	1.01 (0.78-1.31)
809.5-1354.0	101	515	99	507	1.03 (0.78-1.36)
1354.1-2455.5	88	474	111	592	0.80 (0.60-1.06)
>2455.5	107	565	86	455	1.22 (0.92-1.62)
					P for trend = .66
Alcohol as ethanol, g					
<2.60	126	639	120	584	1.04 (0.81-1.33)
2.60-10.9	94	505	99	500	0.98 (0.74-1.30)
11.0-25.6	100	537	79	426	1.25 (0.93-1.68)
>25.6	92	513	111	618	0.81 (0.61-1.07)
					P for trend = .38
Serum factor and category					
α-Tocopherol, mg/L					
<10.2	141	691	121	576	1.21 (0.95-1.54)
10.2-11.5	106	501	104	501	1.02 (0.78-1.33)
11.6-13.1	100	477	122	612	0.79 (0.61-1.03)
>13.1	95	481	98	499	0.97 (0.73-1.28)
					P for trend = .10
β-Carotene, μg/L					
<109	131	652	136	657	0.98 (0.77-1.24)
109-169	106	500	95	463	1.10 (0.83-1.45)
170-260	103	492	116	562	0.86 (0.66-1.13)
>260	102	503	99	488	1.07 (0.81-1.42)
					P for trend = .73
Retinol, μg/L					
<500	139	617	147	665	0.92 (0.73-1.16)
500-575	108	511	108	514	1.03 (0.79-1.34)
576-661	105	506	101	498	1.05 (0.80-1.38)
>661	90	438	90	472	1.00 (0.74-1.34)
					P for trend = .59

*Proportional hazards models were conducted within each subgroup and included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as a continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group. Interaction between intervention (yes, no) and each factor (scored categories) was tested by a separate cross-products term. Number of cases within intervention arm and factor reflect those with available data and may not equal the total.

†Relative risk (95% confidence interval). Two-sided *P* values.

with observations in CARET, where the RRs of lung cancer in the active-treatment group as compared with the placebo group were 1.42 (95% CI = 1.07-1.87) for heavy smokers who were smoking at the time of randomization and 0.80 (95% CI = 0.48-1.31) for heavy smokers who were no longer smoking at the time of randomization. Third, the biologic plausibility of the finding is enhanced by our observation of possibly increasing lung cancer incidence with longer and stronger β-carotene

Table 5. Number of cases, age- and cigarette-adjusted incidence rate (per 10^5 person-years), and relative risk from proportional hazards models for lung cancer by β-carotene intervention and level of base-line dietary intake (daily) and serum vitamins*

	β-Carotene		No β-carotene		
	No. of cases	Rate	No. of cases	Rate	RR (95% CI)†
Total	482	580	412	497	1.16 (1.02-1.33)
Dietary factor and category					
Vitamin E, mg					
<8.10	156	761	114	548	1.40 (1.10-1.78)
8.10-10.6	105	542	94	474	1.14 (0.86-1.51)
10.7-14.5	106	569	80	435	1.27 (0.95-1.70)
>14.5	77	430	89	513	0.85 (0.63-1.15)
					P for trend = .03
β-Carotene, mg					
<1.09	125	604	106	536	1.16 (0.90-1.50)
1.09-1.70	113	584	92	466	1.28 (0.98-1.69)
1.71-2.70	106	561	94	496	1.10 (0.83-1.45)
>2.70	100	535	85	466	1.17 (0.88-1.57)
					P for trend = .84
Carotenoids, mg					
<2.79	139	672	115	565	1.21 (0.95-1.55)
2.79-3.91	118	601	86	449	1.35 (1.02-1.78)
3.92-5.52	99	527	101	527	0.98 (0.74-1.29)
>5.52	88	486	75	422	1.17 (0.86-1.60)
					P for trend = .50
Vitamin C, mg					
<70.5	148	702	118	572	1.26 (0.99-1.61)
70.5-97.1	110	565	114	585	0.98 (0.75-1.27)
97.2-131.1	97	517	74	389	1.31 (0.97-1.77)
>131.1	89	502	71	408	1.21 (0.89-1.66)
					P for trend = .86
Retinol, μg					
<809.5	123	611	106	544	1.14 (0.88-1.48)
809.5-1354.0	113	579	87	444	1.30 (0.99-1.73)
1354.1-2455.5	106	574	93	487	1.15 (0.87-1.52)
>2455.5	102	531	91	487	1.10 (0.83-1.47)
					P for trend = .75
Alcohol as ethanol, g					
<2.60	126	625	120	589	1.05 (0.82-1.35)
2.60-10.9	100	505	93	485	1.04 (0.79-1.38)
11.0-25.6	100	538	79	422	1.27 (0.95-1.71)
>25.6	118	663	85	466	1.41 (1.07-1.87)
					P for trend = .08
Serum factor and category					
α-Tocopherol, mg/L					
<10.2	141	683	121	582	1.21 (0.95-1.55)
10.2-11.5	103	496	107	502	0.97 (0.74-1.27)
11.6-13.1	129	623	93	460	1.33 (1.01-1.73)
>13.1	107	531	86	455	1.20 (0.91-1.59)
					P for trend = .67
β-Carotene, μg/L					
<109	147	709	120	603	1.17 (0.92-1.49)
109-169	109	539	92	432	1.23 (0.93-1.62)
170-260	116	554	103	499	1.13 (0.86-1.47)
>260	109	529	92	455	1.18 (0.89-1.55)
					P for trend = .90
Retinol, μg/L					
<500	158	714	128	570	1.22 (0.96-1.54)
500-575	118	562	98	470	1.24 (0.95-1.62)
576-661	106	500	100	503	1.02 (0.78-1.34)
>661	99	503	81	413	1.23 (0.92-1.65)
					P for trend = .70

*Proportional hazards models were conducted within each subgroup and included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as a continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group. Interaction between intervention (yes, no) and each factor (scored categories) was tested by a separate cross-products term. Number of cases within intervention arm and factor reflect those with available data and may not equal the total.

†Relative risk (95% confidence interval). Two-sided *P* values.

supplementation. In contrast, the lack of a dose–response association between increased on-study serum β-carotene concentrations and lung cancer incidence in the β-carotene group does not support a direct effect.

How β-carotene supplementation might increase lung cancer incidence is speculative. β-Carotene has exhibited pro-oxidant properties under certain conditions such as high (albeit non-physiologic) O_2 pressures (25) or could react with free-radical

Table 6. Number of cases and relative risk for α-tocopherol and β-carotene intervention from proportional hazards multivariate models* for lung cancers occurring after 3 years by duration of intervention†

Duration of intervention, y	No. of cases	RR (95% CI)‡ α-Tocopherol versus no α-tocopherol	RR (95% CI)‡ β-Carotene versus no β-carotene
<1	78	0.96 (0.61-1.50)	0.91 (0.59-1.43)
1-3	50	0.98 (0.56-1.71)	1.37 (0.78-2.40)
>3	404	0.90 (0.74-1.10)	1.31 (1.08-1.59)
		P for trend = .77	*P* for trend = .23

*Within each category, a relative risk was calculated from proportional hazards models that included age, number of cigarettes smoked daily, years of cigarette smoking, body mass index (each factor as continuous variable), and indicator variables (0, 1) for α-tocopherol and β-carotene intervention group.

†Participants who dropped out of the study within the first 3 years and developed lung cancer during that time or within 6 months of withdrawing were excluded. To reduce the possible influence of lung cancer having caused the subjects in the two early dropout categories to become noncompliant, we examined only the relative risks after 3 years of follow-up.

‡Relative risk (95% confidence interval). Two-tailed *P* values.

species of oxygen or nitrogen to produce local lipid peroxidation and genotoxicity in the lung (or other tissues). Alternatively, it might in some way enhance the effective exposure of the lung to the carcinogens in tobacco smoke, adversely alter DNA repair, or reduce the effectiveness of immune scavenging functions such as phagocyte-generated reactive oxidants through its free-radical-quenching properties (*8*). Tissue-specific antioxidant status could be altered through changes in the absorption, metabolism, or balance of other potentially beneficial substances such as carotenoids by supplemental β-carotene (*26-28*). β-Carotene might also have acted through its conversion to retinol, in that retinol (or related compounds) has been postulated to promote carcinogenesis, with alcohol thought to potentiate such an effect in certain organs (*29*). Our base-line data for retinol do not support a positive association with lung cancer, however; instead, they suggest lower incidence with higher retinol status. Whether serum retinol (or other carotenoids) was altered by chronic β-carotene supplementation is now under investigation.

Of potential mechanistic importance is the apparent interaction between β-carotene supplementation and alcohol consumption in increasing lung cancer risk, which is a new finding. Studies in humans and baboons have shown ethanol-related alterations of carotenoid (or vitamin A) metabolism (*30-32*), as well as hepatocellular toxicity in response to β-carotene supplementation combined with extremely high alcohol intake (i.e., 50% of calories as ethanol) (*32*). At present, however, there is no evident mechanism to explain how the interaction of β-carotene and alcohol might promote lung cancer, and this finding will require examination in other studies.

Although most animal studies support a tumor inhibitory effect for β-carotene (*33*), two more recent experiments (*34,35*) suggest a tumor promotional influence for supplemental β-carotene. The first study (*34*) showed that high daily doses of β-carotene accelerated 7,12-dimethylbenz[*a*]anthracene/12-*O*-tetradecanoylphorbol-13-acetate-induced skin papilloma formation and increased tumor yield (i.e., tumors per animal) without increasing incidence (i.e., number of animals having one or more tumors). In the second experiment (*35*), the incidence of respiratory tract carcinomas was increased in benzo[*a*]pyrene-treated hamsters fed supplemental β-carotene, and there was no change in the time to tumor occurrence. Although the underlying mechanism(s) for the β-carotene effect will require further study, considering the long smoking history of the participants and the higher occurrence of lung cancer already seen after only a few years of β-carotene supplementation, it is more likely that β-carotene causes progression of latent lung cancer than that it initiates carcinogenesis. Post-intervention follow-up of the ATBC Study population and other trials, along with more basic research, should help shed light on this.

The findings from the ATBC Study and now CARET highlight the conflicting interpretations resulting from the observational as opposed to the interventional research on β-carotene and lung cancer. Observational studies consistently link low β-carotene status with increased risk of lung cancer; indeed, this inverse association is demonstrated in our results for base-line dietary and serum β-carotene. Despite this finding, intervention with supplemental β-carotene increased lung cancer incidence. This apparent paradox can be interpreted in several ways. Serum levels and "usual" diet at study entry probably represent long-term, possibly lifelong, exposure to intake within the normal dietary range of β-carotene. Higher dietary intake over a prolonged period may, therefore, lower lung cancer risk. In contrast, the β-carotene intervention studies used high doses of β-carotene for relatively short periods. In the ATBC Study, for example, the 20-mg supplement was 12 times higher than the 1.7-mg median daily dietary intake of β-carotene and resulted in a 17-fold increase in serum levels, from 170 μg/L at base line to 3000 μg/L during the study. It is, therefore, possible that the observational and intervention studies are both correct. Lung cancer risk may be elevated at low dietary intake and reduced when dietary intake is moderate or high but increased at the markedly elevated levels associated with supplementation in the trials (i.e., a U-shaped relationship). Alternatively, β-carotene levels measured in blood or estimated from dietary intake may merely be serving as a marker for one or more other substances that are the actual protective agents, while β-carotene itself may have little or no biologic effect at levels associated with normal dietary intake. The presence of several carotenoids (e.g., β-carotene and lutein/zeaxanthin) along with numerous other phytochemicals in β-carotene-rich fruits and vegetables suggests that such potential benefit could be due, in part, to one or more of these several components, singly or in combination, as has been suggested by some studies (*36,37*). It is also conceivable that high β-carotene intake or serum concentrations are general indicators of other beneficial dietary or protective lifestyle practices or, conversely, of differences in exposures to harmful or carcinogenic factors.

In summary, we observed no benefit in lung cancer prevention for either agent in this population of long-term cigarette smokers. Our analyses are consistent with a harmful effect of β-carotene on lung cancer that may have been limited to participants who consumed greater amounts of alcohol and possibly to those who smoked heavily. The results suggest that high-dose β-carotene supplementation should be avoided by such smokers.

Some of the issues in need of further investigation are identification of mechanisms of action, the relevance to nonsmoking populations and to supplementation with lower β-carotene doses, effects on morbidity and mortality from other causes, and the joint effects of β-carotene and alcohol on lung cancer.

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Notes

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