

Predictors of Lung Cancer among Asbestos-exposed Men in the β -Carotene and Retinol Efficacy Trial

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Despite numerous published studies, debate continues regarding the risk of developing lung cancer among men exposed occupationally to asbestos, particularly those without radiographic or functional evidence of asbestosis. The β -Carotene and Retinol Efficacy Trial (CARET), a study of vitamin supplementation for chemoprevention of lung cancer, has followed 4,060 heavily exposed US men for 9–17 years. Lung cancer incidence for 1989–2002 was analyzed using a stratified proportional hazards model. The study confirmed excessive rates of lung cancer among men with radiographic asbestosis. Comparison of study arms revealed a strong, unanticipated synergy between radiographic profusion category and the active intervention. In the large subgroup of men with normal lung parenchyma on chest radiograph at baseline, there was evidence of exposure-related lung cancer risk: Men with more than 40 years' exposure in high-risk trades had a risk approximately fivefold higher than men with 5–10 years, after adjustment for covariates. The effect in these men was independent of study intervention arm, but pleural plaques on the baseline radiograph and abnormal baseline flow rate were strong independent predictors of subsequent lung cancer. Residual confounding by subclinical asbestosis, exposure to unmeasured lung carcinogens, or differences in smoking are unlikely to explain these observations better than a carcinogenic effect of asbestos per se.

asbestos; asbestosis; beta carotene; clinical trial [publication type]; lung neoplasms; occupational exposure; vitamin A

Abbreviations: CARET, β -Carotene and Retinol Efficacy Trial; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ILO, International Labour Organization.

Numerous lung cancer cohort studies of men exposed occupationally to asbestos in various industries and trades have been published since Doll's groundbreaking observation in 1955 (1–12). Collectively, these studies have established that asbestos causes lung cancer in humans, although the dose-response relation varies substantially from cohort to cohort. Toxicologists, environmental scientists, and epide-

miologists have proffered competing explanations for observed differences, including differences in fiber type, fiber dimensions, and the presence of environmental cofactors (5, 13–16). Substantial synergy with tobacco smoke has been supported in most studies (17–21). Although several case series on clinically characterized subjects have supplemented this epidemiologic literature (22–24), the utility of

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available data for clinical management of the millions of formerly exposed survivors, and the even larger numbers with environmental exposure (25), remains limited. Using various strategies for retrospective exposure quantification, these studies have confirmed high risk in the most heavily exposed persons, especially those with radiographically apparent asbestosis, but findings differ for those with lesser exposure. Studies of the predictive value of pleural plaques have yielded contradictory results (26–28). The predictive role of lung function in asbestos-exposed subjects remains unexplored.

Particularly controversial is the risk of lung cancer among persons who do *not* have clinical evidence of asbestosis. As Cullen (13) has reviewed in detail, some investigators have suggested that such subjects remain at excess risk for lung cancer proportional to their exposure (4, 26, 29–32). Others have argued that lung cancer in this setting is a complication of asbestosis, not a primary consequence of exposure in the absence of fibrosis (33–35). If confirmed, such a theory would downgrade estimates of lung cancer risk among persons exposed to asbestos at doses too low to cause fibrosis, and would provide the basis for reassurance to more heavily exposed persons whose radiographs remained normal or demonstrated only nonmalignant pleural changes.

To address some of these questions, we analyzed outcomes among 4,060 asbestos-exposed men followed prospectively for 9–17 years. These men were recruited from diverse jobs and occupations involving asbestos exposure as participants in the β -Carotene and Retinol Efficacy Trial (CARET). CARET is a multicenter randomized, double-blinded, placebo-controlled trial of the efficacy of daily pharmacologic doses of vitamin A and β -carotene in preventing lung cancer among heavy smokers and asbestos workers that was begun in the mid-1980s (36). The intervention was discontinued 21 months ahead of schedule in 1996 when accrued evidence proved that the vitamins did not prevent lung cancer and strongly suggested *increased* risk of lung cancer, an effect most pronounced among the asbestos workers (37, 38). Follow-up of participants has continued to the present.

In this analysis, we addressed the following questions:

1. Among men with asbestosis based on standardized (International Labour Organization (ILO)) reading of a plain chest radiograph, what is the relative risk of lung cancer, adjusted for both intensity and timing of smoking?
2. Among men *without* radiographic evidence of fibrosis of the lung parenchyma, is there evidence of increased lung cancer risk? If so, how does this risk vary by occupational history, the presence or absence of pleural plaques, and baseline lung function?
3. Do any of these characteristics interact with the intervention vitamins?

Because CARET recruitment was designed to select participants at the highest possible risk of lung cancer, men with less than 5 years in a heavily exposed occupation and those who had never smoked or had quit smoking more than 15 years before study entry were excluded (except in a small pilot phase); women were also excluded, since too few were deemed potentially eligible. For this reason, we are unable to

address the issue of risk among women, nonsmokers, or men with brief or low-level asbestos exposures.

MATERIALS AND METHODS

Recruitment and enrollment

The strategies used for recruitment, enrollment, randomization, and follow-up of the 7,965 male heavy smokers and 4,060 asbestos-exposed men in the CARET study have been previously described (39, 40), as have the baseline characteristics of the asbestos-exposed subcohort (41). Asbestos-exposed men were eligible for enrollment during the years 1989–1993 if they were between 45 and 69 years of age, currently smoked or had quit smoking within the previous 15 years, and had documentation of exposure. Exposure was documented by 1) employment in a trade with established regular asbestos exposure and published risk of asbestos-related diseases—insulation, sheet metal work, plumbing, plasterboard application, shipfitting, ship electrical work, boilermaking, or ship scaling—for at least 5 years, starting at least 15 years previously, or 2) occupational asbestos exposure in any job or occupation *and* evidence of radiographic changes consistent with a diagnosis of nonmalignant asbestos-related disease. This included 1) benign pleural disease, defined as thickening or fibrotic plaques on pleural surfaces of the lung bilaterally, and/or 2) asbestosis, defined as diffuse lung scarring based on increased profusion of small irregular shadows bilaterally. Asbestos-exposed men were recruited at five US study centers: Seattle, Washington; Baltimore, Maryland; Portland, Oregon; New Haven, Connecticut; and San Francisco, California. A total of 3,244 men were enrolled; most were referred by occupational health clinics, employers, unions, or compensation lawyers or responded to advertisements. Previously, between 1985 and 1988, 816 men had been enrolled in a pilot phase of the study in Seattle using similar criteria but a wider age span (45–74 years) and no smoking requirement. All participants signed consent forms that had been reviewed by a human subjects protection committee before baseline evaluation.

Baseline evaluation

Prior to randomization to daily receipt of β -carotene (30 mg) plus retinyl palmitate (25,000 IU) or placebo, participants in the asbestos-exposed cohort had a plain chest radiograph and standardized spirometric measurements taken using methods published previously (41). Briefly, radiographs were interpreted by a single trained “B-reader” at each study center, using ILO standard films to quantify the profusion of small irregular shadows in the lung parenchyma, using a 12-point scale from 0/– to 3/+. Radiographs rated 0/–, 0/0, and 0/1 are considered to provide evidence that lung fibrosis is scant or absent (i.e., normal), whereas those rated 1/0 or higher are considered to provide evidence for asbestosis in exposed men. To evaluate consistency in the readings from center to center, the Seattle center panel reread a sample of 48 films from the individual sites; exact agreement was obtained for 44–50 percent of the films, and agreement within one minor category was obtained for 79–91

percent. There was 88–93 percent agreement on the presence or absence of pleural change (41).

After complete enrollment and randomization, the asbestos-exposed cohort included 34 percent men who qualified by virtue of their work history alone (5 or more years in one of the designated trades), 21 percent who qualified by radiographic criteria alone, and 44 percent who met both types of entry criteria. Approximately 0.5 percent of those randomized were found upon review to be ineligible and were subsequently excluded from the analysis, along with 133 participants from the pilot study who were lifelong nonsmokers and 10 with inadequate baseline information. This left 3,897 participants for these analyses.

Of these subjects, 79 percent had incurred their primary asbestos exposure in one of the designated trades; 21 percent had worked at one or more of 420 different asbestos-exposed jobs in over 260 industries. Because of the dearth of quantitative exposure data from most workplaces, no effort was undertaken to further classify participants by exposure dose, fiber type, or distribution of fiber sizes. Duration of exposure was used instead as a surrogate for dose where appropriate. Radiographic parenchymal changes indicating asbestosis (ILO grade $\geq 1/0$) were found in 39 percent of the participants; 47 percent had pleural abnormalities diagnosed at baseline.

To facilitate internal comparisons within the CARET asbestos cohort and external comparison with the only appropriate reference group—the CARET smoker cohort—we further subdivided the asbestos-exposed cohort by smoking status, eligibility criteria, and baseline radiographic findings (figure 1). Of the asbestos-exposed men, 1,839 also met the more rigorous criteria for eligibility in the heavy-smoker arm of CARET: quitting no less recently than 6 years, having at least 20 pack-years of accumulated tobacco smoking, and being at least 50 years of age at enrollment. This subgroup is identified as the “smoker-eligible participants” to distinguish them from the larger cohort of all asbestos-exposed participants, of whom 2,195 had less than 20 pack-years of smoking, had quit more than 6 years before, or were younger than age 50 at randomization. A second subcohort has been designated “work-history-eligible.” These 3,067 men met the formal occupational exposure criterion for entry, that is, more than 5 years in one of the designated high-risk trades beginning more than 15 years prior to randomization. Excluded from this subcohort were the 830 men exposed in other occupations, who were enrolled on the basis of asbestos-related radiographic changes. Within the work-eligible subcohort, a subset of participants had normal lung parenchyma at baseline (ILO grade $<1/0$). These 2,089 participants constituted the “work-eligible ILO $<1/0$ ” subcohort.

Follow-up

Prior to discontinuation of the active intervention in January 1996, participants were contacted by their local study center three times per year and evaluated in person at least once. During the active phase of the trial, lung function tests were repeated annually but not chest radiographs. After active intervention was stopped, contact remained local but

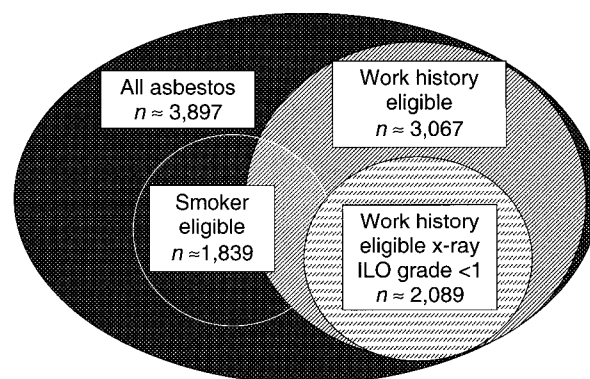


FIGURE 1. Subcohorts delineated within the asbestos exposure cohort of the β -Carotene and Retinol Efficacy Trial (CARET). “Smoker-eligible” participants met separate age and smoking criteria for inclusion in the smoking arm of the CARET study. “Work-history-eligible” participants met entrance criteria for having worked at least 5 years in a designated trade involving high asbestos exposure. Among these persons, a subset of approximately two thirds had no evidence of lung parenchymal asbestosis (International Labour Organization (ILO) grade 0) on the chest radiograph at the time of randomization in CARET.

was reduced to an annual phone call until April 2000. Since then, all follow-up has been performed annually by mail and phone by the staff of the CARET Coordinating Center in Seattle. All reports of incident cancer or cancer mortality are confirmed by the CARET Endpoints Committee through review of clinical records and pathology reports. The current analysis included follow-up information that was complete through October 31, 2002.

Statistical analysis

Stratified Cox proportional hazards models were used to obtain lung cancer relative risk estimates and 95 percent confidence intervals. The time axis in the models was the time to diagnosis of lung cancer or the date on which the participant was last known to be alive. Mean length of follow-up was 10 years among asbestos-exposed participants and 9 years in the heavy-smoker cohort. The assumption of proportional hazards was assessed with time-dependent covariates (the product of log-transformed time and the factor of interest) and examination of log cumulative hazard plots. In all models, data were stratified on enrollment period (pilot or efficacy phase) to account for differences in baseline hazards due to changes in eligibility criteria. Models included adjustment for intervention arm assignment (vitamin A + β -carotene vs. placebo), baseline smoking status (current smoker vs. former smoker), pack-years of smoking (<40 , 40 – 60 , or >60), and age (<55 , 55 – 64 , or ≥ 65 years). Age and pack-years were modeled as grouped linear variables, constructed by assigning ordinal scores to the categories, and fitted as continuous variables.

Analyses restricted to the asbestos-exposed workers were further stratified on enrollment center (except in smoker-eligible comparisons, because only two of the six CARET study centers recruited participants for both the asbestos and

TABLE 1. Demographic characteristics of participants by exposure population and lung cancer status, β -Carotene and Retinol Efficacy Trial, 1989–2002

Characteristic	Asbestos-exposed cohort								Smoker cohort#	
	All asbestos-exposed subjects*		Work-history-eligible†		Work-history-eligible with ILO‡ grade <1§		Smoker-eligible¶			
	Total	LC‡ cases	Total	LC cases	Total	LC cases	Total	LC cases	Total	LC cases
No. of participants	3,897	241	3,067	197	2,089	97	1,839	165	7,924	542
Mean age (years) (mean (SD)‡)	57 (7)	61 (6)	56 (7)	60 (7)	55 (7)	60 (7)	59 (6)	61 (5)	58 (5)	61 (5)
Age group (years) (no. (%))										
<55	1,585 (41)	46 (19)	1,360 (44)	42 (21)	1,036 (50)	25 (26)	531 (29)	26 (10)	2,557 (32)	81 (15)
55–64	1,616 (41)	114 (47)	1,205 (39)	92 (47)	764 (37)	45 (46)	980 (53)	92 (56)	4,150 (52)	322 (59)
≥65	696 (18)	81 (34)	502 (16)	63 (32)	289 (14)	27 (28)	328 (18)	47 (28)	1,217 (15)	139 (26)
Smoking status at enrollment (no. (%))										
Current smoker	1,548 (40)	127 (53)	1,235 (40)	103 (52)	814 (39)	48 (49)	1,105 (60)	113 (68)	5,134 (65)	404 (75)
Former smoker	2,349 (60)	114 (47)	1,832 (60)	94 (48)	1,275 (61)	49 (51)	734 (40)	52 (32)	2,790 (35)	138 (25)
Years since quitting smoking (former smokers) (no. (%))										
0–4	636 (27)	38 (33)	480 (26)	31 (33)	331 (26)	15 (31)	476 (65)	35 (67)	2,020 (72)	108 (78)
5–6	365 (16)	18 (16)	274 (15)	13 (14)	187 (15)	6 (12)	258 (35)	17 (33)	770 (28)	30 (22)
7–9	351 (15)	16 (14)	281 (15)	13 (14)	196 (15)	9 (18)				
10–14	595 (25)	31 (27)	468 (26)	28 (30)	324 (25)	15 (31)				
>14	402 (17)	11 (10)	329 (18)	9 (10)	237 (19)	4 (8)				
Mean pack-years of smoking (mean (SD))	43 (24)	55 (26)	42 (24)	54 (26)	40 (24)	56 (29)	53 (23)	61 (27)	53 (22)	61 (22)
Pack-years of smoking (no. (%))										
≤40	2,051 (53)	79 (33)	1,652 (54)	65 (33)	1,186 (57)	32 (33)	618 (34)	38 (23)	2,522 (32)	97 (18)
41–60	1,127 (29)	82 (34)	874 (28)	69 (35)	556 (27)	30 (31)	678 (37)	58 (35)	3,016 (38)	222 (41)
>60	719 (18)	80 (33)	541 (18)	63 (32)	347 (17)	35 (36)	543 (30)	69 (42)	2,386 (30)	223 (41)
Mean years of asbestos exposure (mean (SD))	27 (10)	29 (11)	27 (10)	29 (10)	26 (10)	29 (10)	28 (10)	30 (10)	3 (9)	4 (10)
Mean years in a high-risk trade (mean (SD))	19 (13)	22 (14)	24 (10)	27 (11)	23 (10)	27 (10)	19 (14)	22 (15)	<1 (<1)	<1 (<1)

* Excludes 163 participants: never smokers ($n = 133$), participants who did not meet the asbestos eligibility criteria ($n = 24$), participants with an unknown number of pack-years of smoking ($n = 8$), and/or participants who were missing a baseline radiograph ($n = 2$).

† Excludes 993 participants: 830 who were eligible on the basis of radiographic findings only, 133 never smokers, 24 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

‡ ILO, International Labour Organization; LC, lung cancer; SD, standard deviation.

§ ILO classification of radiographic category 0. Excludes 1,971 participants: 978 with a profusion rating greater than 0/1, 830 who were eligible on the basis of radiographic findings only, 133 never smokers, 24 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

¶ Excludes 2,195 participants who did not meet the heavy-smoker eligibility criteria (≤ 6 years since quitting smoking, ≥ 20 pack-years of smoking, and age 50–69 years). Also excludes 24 participants who did not meet the asbestos eligibility criteria and two participants who were missing a baseline radiograph.

Excludes 12 participants who did not meet the heavy-smoker eligibility criteria (see above footnote) and 29 participants who met the asbestos eligibility criteria.

heavy-smoker cohorts) and included additional adjustment for years since quitting smoking (as a categorical variable: current smoking or 0–4, 5–9, 10–14, or >14 years since quitting). Time since last smoking was excluded from the final smoker-eligible model, because almost 80 percent of the smoker-eligible participants had smoked within 2 years of enrollment.

Asbestos-related predictors (years in a high-risk trade, years since last asbestos exposure, primary trade, presence of pleural plaques, and ILO grade) were fitted simultaneously in analyses including the asbestos cohort only. For the smoker-eligible analyses, the asbestos-related variables were assessed in separate Cox models, with CARET's male

heavy-smoker population serving as the referent in each. The association of lung function with lung cancer incidence was examined in the work-eligible ILO <1/0 subcohort by modeling forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) and percent predicted FEV₁ and FVC as categorical variables (≥ 80 percent, 70–79 percent, 60–69 percent, or <60 percent), adjusted for work history and presence of pleural abnormalities. Because lung function may be in the causal pathway between asbestos exposure and lung cancer incidence (42), we also examined estimates unadjusted for work history (data not shown); no appreciable differences were observed. We performed likelihood ratio tests to test for linear trend across categories where appro-

TABLE 2. Radiographic predictors of lung cancer incidence among asbestos-exposed participants in the smoker-eligible subcohort,* β -Carotene and Retinol Efficacy Trial, 1989–2002

	Total no.	No. of lung cancer cases	Relative risk†	95% confidence interval	p value
Risk population					
Heavy smoker	7,924	542	1.00		
Asbestos-exposed	1,839	165	1.24	1.04, 1.47	0.02
Pleural abnormality‡					0.01
Heavy smoker	7,924	542	1.00		
Negative	953	71	1.05	0.82, 1.34	0.71
Positive	886	94	1.44	1.15, 1.79	0.001
Profusion rating§					
Major categories					<0.0001¶
Heavy smoker	7,924	542	1.00		
0/– to 0/1	1,007	69	0.98	0.76, 1.26	0.89
1/0 to 1/2	769	83	1.42	1.12, 1.79	0.003
2/1 to 2/3	47	8	2.35	1.17, 4.72	0.02
3/2 to 3/+	16	5	4.42	1.83, 10.69	0.001
Minor categories					<0.0001¶
Heavy smoker	7,924	542	1.00		
0/–	2	0	0.00		
0/0	446	26	0.89	0.60, 1.32	0.57
0/1	559	43	1.05	0.77, 1.44	0.75
1/0	510	52	1.34	1.01, 1.79	0.04
1/1	207	24	1.52	1.01, 2.29	0.04
1/2	52	7	1.72	0.82, 3.63	0.15
2/1	25	4	2.17	0.81, 5.81	0.12
2/2	15	4	3.45	1.29, 9.24	0.01
2/3	7	0	0.00		
3/2	7	1	1.82	0.26, 13.0	0.55
3/3	7	3	5.78	1.85, 18.05	0.002
3/+	2	1	15.62	2.17, 112.3	0.006

* Excludes 2,221 asbestos-exposed participants: 2,199 who did not meet the heavy-smoker eligibility criteria, 20 who did not meet the asbestos eligibility criteria, and two who did not have a baseline radiograph. Also excludes 41 heavy smokers: 12 who did not meet the heavy-smoker eligibility criteria and 29 who met the asbestos eligibility criteria.

† Risk estimate from a Cox regression model with stratification by cohort and adjustment for age (<55, 55–64, or ≥65 years), smoking status at baseline (current smoker or former smoker), pack-years of smoking (<40, 40–60, or >60), and intervention arm.

‡ Presence of bilateral pleural thickening or plaques on radiograph at baseline, with or without calcification.

§ Density of small irregular shadows in the lung fields using the International Labour Organization's 12-point rating scale.

¶ Test for trend using a grouped linear variable.

appropriate and to test whether the associations between asbestos-related measures and lung cancer risk were modified by age, smoking status, pack-years, and intervention assignment. Intervention assignment-specific relative risk estimates were obtained from models that included cross-product interaction terms between intervention arm and each predictor of interest. The association between pack-years and years of working in a high-risk trade was assessed with Pearson and Spearman correlations; only the Pearson estimates are

presented, since differences between the two were negligible. All significance tests were two-sided. Analyses were performed using SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 241 cases of lung cancer were observed among the 3,897 men in the asbestos-exposed cohort, giving an

TABLE 3. Radiographic predictors of lung cancer incidence among all asbestos-exposed participants,* β -Carotene and Retinol Efficacy Trial, 1989–2002

Profusion rating†	Overall				Active				Placebo			
	Total no.	No. of LC‡ cases	RR‡,§	95% CI‡	Total no.	No. of LC cases	RR§	95% CI	Total no.	No. of LC cases	RR§	95% CI
0/– or 0/0	1,181	40	1.00		609	17	1.00		572	23	1.00	
0/1	1,184	69	1.48	0.99, 2.22	574	27	1.40	0.76, 2.60	610	42	1.55	0.92, 2.61
1/0 to 1/2	1,424	113	1.93	1.32, 2.84	728	66	2.72	1.57, 4.73	696	47	1.37	0.82, 2.31
2/1 to 2/3	84	12	2.90	1.47, 5.73	36	7	5.25	2.12, 13.0	48	5	1.65	0.61, 4.48
3/2 to 3/+	24	7	6.76	2.80, 16.3	15	6	12.45	4.47, 34.6	9	1	1.92	0.25, 14.9
<i>p</i> for trend¶			<0.0001				<0.0001				0.25	
<i>p</i> for interaction#							0.001					

* Excludes 163 participants: 133 never smokers, 20 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

† Density of small irregular shadows in the lung fields using the International Labour Organization's 12-point rating scale.

‡ LC, lung cancer; RR, relative risk; CI, confidence interval.

§ Risk estimate from a Cox regression model with stratification by cohort and study center and inclusion of the following covariates: age (<55, 55–64, or ≥65 years), years since quitting smoking (current smoking or 0–4, 5–9, 10–14, or >14 years), pack-years of smoking (<40, 40–60, or >60), trade (eight specified high-risk trades and an “other” category), intervention arm (active vitamins or placebo), years of working in a high-risk trade (<10, 11–20, 21–30, 32–40, or >40), presence of pleural abnormality (yes/no), and years since last asbestos exposure (0, 1–5, 6–10, 11–15, or >15).

¶ Test for trend using a grouped linear variable.

Test of interaction for intervention arm assignment × profusion rating coded as a grouped linear variable.

overall incidence rate of 5.9 per 1,000 person-years (95 percent confidence interval: 5.2, 6.7). The demographic, smoking, and occupational histories of men in the cohort and the lung cancer cases, as well as the three subcohorts (figure 1), are shown in table 1. Also shown for comparison are the same parameters for the 7,924 male heavy smokers; 29 were found to have asbestos exposure sufficient to be eligible for the asbestos cohort and were excluded.

As anticipated, men in the asbestos-exposed smoker-eligible subcohort had a significantly higher rate of lung cancer than their counterpart smokers (table 2). Baseline radiographic status was a strong predictor, as is shown in the same table. Participants with pleural plaques or other asbestos-related pleural changes had a 44 percent higher risk of lung cancer than the unexposed heavy smokers; the subgroup without plaques did not have significantly higher risk. Parenchymal changes on radiograph were associated with progressively increasing relative risk, evident at the lowest level of pulmonary fibrosis by radiograph: ILO profusion ratings 1/0–1/2. The relative risk of men in this group as compared with the heavy smokers without asbestos exposure was 1.42. Men with advanced asbestosis (grade 3) had 4.4 times' greater risk; those with grade 2 changes upon radiograph had intermediate risk.

To better estimate risk among men with normal lung parenchyma on the baseline radiograph, we performed an internal analysis of the entire asbestos-exposed cohort. Table 3 shows the relative risk of lung cancer in the entire cohort, by ILO category. After adjustment for age, pack-years of smoking, years since quitting smoking, presence of pleural abnormalities, and high-risk trade exposure and type, the risk of lung cancer in participants with radiographs graded 0/1 (borderline normal) was 48 percent higher than in those

with ILO grade 0/0—an excess of borderline statistical significance. While the numbers of participants in the higher categories dwindled, there was an increase in risk with rising category, as in the smoker-eligible subcohort. Table 3 demonstrates that when data were stratified across treatment arms, there was a strong and previously unexpected “synergy” between asbestosis grade and the active intervention arm ($p < 0.0001$). Among participants receiving placebo, only a small, nonsignificant risk gradient was seen with rising profusion score, whereas among those taking active vitamins, the gradient was steep and significant, rising to over 12-fold in those with advanced (ILO grade ≥3/2) radiographic changes.

To evaluate the predictive significance of exposure history per se independently of radiographic change, we assessed the subcohort of participants who were eligible for the study on the basis of having worked for 5 or more years in one of the preassigned “high-risk trades,” excluding the 830 participants who had entered the study on the basis of an asbestos-related radiographic abnormality at baseline. Among these exposure-eligible participants, there was a significant predictive effect of years in the trade (table 4), with risk rising to 2.3 from the least exposed categories to the most exposed. Intervention arm did not modify this finding. The effect of radiograph in this subcohort mirrors that seen in the full cohort. Variation by year of last exposure shows significantly increased risk among persons last exposed 5 or more years prior to randomization, which is consistent with likely heavier exposure per year in earlier years.

Given the uncertainty about whether asbestos exposure, as opposed to asbestosis, presents a quantifiably increased risk of lung cancer, we examined the exposure surrogate—years of exposure in a high-risk trade—in the subgroup of

TABLE 4. Predictors of lung cancer incidence among work-history-eligible asbestos-exposed participants,* β -Carotene and Retinol Efficacy Trial, 1989–2002

	Overall				Active				Placebo			
	Total no.	No. of LC† cases	RR‡,§	95% CI†	Total no.	No. of LC cases	RR§	95% CI	Total no.	No. of LC cases	RR§	95% CI
Years in a high-risk trade												
<10	410	19	1.00		219	11	1.00		191	8	1.00	
11–20	776	39	1.26	0.72, 2.21	390	23	1.42	0.67, 3.01	386	16	1.10	0.46, 2.59
21–30	1,003	59	1.60	0.92, 2.77	491	25	1.26	0.60, 2.67	512	34	1.94	0.88, 4.30
31–40	722	59	1.68	0.92, 3.08	362	30	1.32	0.61, 2.88	360	29	1.96	0.85, 4.54
>40	156	21	2.31	1.12, 4.76	72	9	1.86	0.70, 4.93	84	12	3.05	1.15, 7.89
<i>p</i> for trend¶			0.02				0.40				0.008	
<i>p</i> for interaction#							0.14					
Pleural abnormality**												
Negative	1,769	86	1.00		878	40	1.00		891	46	1.00	
Positive	1,298	111	1.43	1.06, 1.94	656	58	1.50	0.97, 2.31	642	53	1.34	0.89, 2.03
<i>p</i> for main effect¶			0.02				0.07				0.17	
<i>p</i> for interaction#							0.72					
Profusion rating††												
0/– to 0/1	2,089	97	1.00		1,036	37	1.00		1,053	60	1.00	
1/0 to 1/2	902	85	1.63	1.20, 2.22	462	50	2.52	1.63, 3.91	440	35	1.10	0.71, 1.69
2/1 to 2/3	57	8	1.92	0.89, 4.13	24	5	4.21	1.59, 11.1	33	3	0.91	0.28, 3.03
3/2 to 3/+	19	7	6.23	2.63, 14.8	12	6	13.0	4.90, 34.7	7	1	1.59	0.21, 12.1
<i>p</i> for trend¶			<0.0001				<0.0001				0.70	
<i>p</i> for interaction#							0.0002					
Years since last asbestos exposure												
0	868	38	1.00		436	16	1.00		432	22	1.00	
1–5	587	35	0.96	0.59, 1.54	281	16	1.02	0.50, 2.08	306	19	0.89	0.48, 1.68
6–10	475	49	1.78	1.11, 2.84	237	26	2.23	1.14, 4.36	238	23	1.53	0.82, 2.86
11–15	748	45	1.61	0.93, 2.80	377	23	1.80	0.87, 3.74	371	22	1.46	0.73, 2.92
>15	389	30	1.78	1.00, 3.20	203	17	2.52	1.16, 5.46	186	13	1.31	0.61, 2.80
<i>p</i> for trend¶			0.01				0.008				0.20	
<i>p</i> for interaction#							0.23					

* Excludes 993 participants: 830 who were eligible on the basis of radiographic findings only, 133 never smokers, 20 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

† LC, lung cancer; RR, relative risk; CI, confidence interval.

‡ Risk estimate from a Cox regression model with stratification by cohort and study center and inclusion of the following covariates: age (<55, 55–64, or ≥65 years), years since quitting smoking (current smoking or 0–4, 5–9, 10–14, or >14 years), pack-years of smoking (<40, 40–60, or >60), trade (eight specified high-risk trades and an “other” category), intervention arm (active vitamins or placebo), and the asbestos-related predictors defined above.

§ Risk estimate from a Cox regression model as defined above that also included interaction terms for intervention arm assignment × profusion rating and arm × predictor of interest.

¶ Test for trend using a grouped linear variable.

Test of interaction for intervention arm assignment × predictor of interest coded as a grouped linear variable.

** Presence of bilateral pleural thickening or plaques upon radiograph, with or without calcification.

†† Density of small irregular shadows in the lung fields using the International Labour Organization's 12-point rating scale.

exposure-history-eligible participants who had normal radiographs on the ILO scale (ILO grade <0/1) (table 5). In this subcohort, the gradient of increased risk with increasing duration of exposure was stepwise and significant, reaching a fivefold excess in the most heavily exposed groups versus the least heavily exposed after adjustment for the covariates. Pleural change remained predictive; it was associated with approximately a doubling of lung cancer risk after adjustment. Neither of these results seemed to have been modified by the study intervention

vitamins; if anything, trends were more conspicuous among the participants receiving placebo.

We conducted additional analyses to address two of the more plausible explanations for the exposure-years-response trend among persons with normal lung parenchyma upon radiograph: 1) residual confounding by tobacco—that is, more smoking among men in the groups with longer exposure, even after adjustment for pack-years—and 2) misclassification of “asbestosis” status—that is, inclusion of more participants with radiographically undetected asbestosis in

TABLE 5. Predictors of lung cancer incidence among work-history-eligible asbestos-exposed participants with an International Labour Organization rating less than 1/0,* β -Carotene and Retinol Efficacy Trial, 1989–2002

	Overall				Active				Placebo			
	Total no.	No. of LC† cases	RR‡,§	95% CI†	Total no.	No. of LC cases	RR‡	95% CI	Total no.	No. of LC cases	RR‡	95% CI
Years in a high-risk trade												
<10	272	6	1.00		152	4	1.00		120	2	1.00	
11–20	570	23	2.07	0.82, 5.19	285	10	1.59	0.49, 5.17	285	13	3.08	0.68, 13.9
21–30	720	30	2.50	0.97, 6.42	344	9	1.36	0.40, 4.71	376	21	4.55	1.02, 20.2
31–40	441	26	3.15	1.12, 8.85	212	10	2.19	0.61, 7.94	229	16	4.98	1.05, 23.8
>40	86	12	5.17	1.61, 16.6	43	4	2.29	0.48, 10.9	43	8	10.92	2.07, 57.7
<i>p</i> for trend§			0.007				0.23				0.003	
<i>p</i> for interaction¶												
Pleural abnormality#												
Negative	1,325	47	1.00		654	19	1.00		671	28	1.00	
Positive	764	50	1.91	1.25, 2.92	382	18	1.91	0.98, 3.73	382	32	1.91	1.12, 3.27
<i>p</i> for trend§			0.003				0.06				0.02	
<i>p</i> for interaction¶							0.99					
Years since last asbestos exposure												
0	611	18	1.00		310	8	1.00		301	10	1.00	
1–5	370	17	1.07	0.53, 2.16	174	4	0.55	0.16, 1.88	196	13	1.49	0.64, 3.50
6–10	313	25	2.10	1.07, 4.10	153	11	1.93	0.73, 5.06	160	14	2.18	0.91, 5.22
11–15	539	21	1.64	0.74, 3.62	264	8	1.54	0.52, 4.55	275	13	1.74	0.66, 4.58
>15	256	16	2.79	1.23, 6.34	135	6	2.48	0.76, 8.04	121	10	3.08	1.14, 8.30
<i>p</i> for trend§			0.01				0.05				0.04	
<i>p</i> for interaction¶							0.82					

* Excludes 1,971 participants: 978 with a profusion rating greater than 0/1, 830 who were eligible on the basis of radiographic findings only, 133 never smokers, 20 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

† LC, lung cancer; RR, relative risk; CI, confidence interval.

‡ Risk estimate from a Cox regression model with stratification by cohort and study center and inclusion of the following covariates: age (<55, 55–64, or ≥65 years), years since quitting smoking (current smoking or 0–4, 5–9, 10–14, or >14 years), pack-years of smoking (<40, 40–60, or >60), trade (eight specified high-risk trades and an “other” category), intervention arm (active vitamins or placebo), and the asbestos-related predictors defined above.

§ Test for trend using a grouped linear variable.

¶ Test of interaction for intervention arm assignment × predictor of interest coded as a grouped linear variable.

Presence of bilateral pleural thickening or plaques upon radiograph, with or without calcification.

the groups with longer exposure. Neither of these explanations appeared highly likely. The Pearson correlation between pack-years and asbestos-years, measured continuously, was only 0.09. Moreover, the mean values and standard errors for all measures of lung function (data not shown) were almost identical among the groups. While low-normal mean values suggest that there may have been some cases of subclinical asbestosis within each subgroup, the absence of any gradient by exposure length renders residual confounding by subradiographic asbestosis unlikely.

Finally, we evaluated the role of baseline lung function in subsequent lung cancer risk in this work-eligible, ILO <1/0 subcohort. As is shown in table 6, decreasing values of FEV₁, FVC, and (especially) FEV₁:FVC ratio were strongly associated with future lung cancer risk, suggesting an effect of preexisting obstructive lung disease. The risk gradients associated with these functional changes in men without asbestosis appeared to be independent of intervention assignment, with the possible exception of the small group with FVC values less than 60 percent predicted.

DISCUSSION

Observational analysis of data from this large, randomized, controlled chemoprevention trial appears to confirm excessive rates of lung cancer among men with asbestosis and demonstrates for the first time synergy between the lung parenchymal changes and the intervention vitamins. Among participants with normal lung parenchyma on chest radiograph, there was also evidence of exposure-related risk; men with more than 40 years of exposure in high-risk trades had a risk fivefold higher than men with 5–10 years of exposure after adjustment for smoking and other risk factors. The presence of pleural plaques and obstructive lung disease at baseline was also associated with significantly increased risk of lung cancer. In the subcohort of men who were free of radiographic asbestosis, no interaction with study vitamins was evident.

Although this population was recruited for a randomized trial and, as such, differs from typical populations identified

TABLE 6. Lung-function predictors of lung cancer incidence among work-history-eligible asbestos-exposed participants with an International Labour Organization rating less than 1/0 and valid baseline spirometry measures available,* β -Carotene and Retinol Efficacy Trial, 1989–2002

	Overall				Active				Placebo			
	Total no.	No. of LC† cases	RR‡,§	95% CI†	Total no.	No. of LC cases	RR‡	95% CI	Total no.	No. of LC cases	RR‡	95% CI
% predicted FEV ₁ †												
≥80	1,064	23	1.00		515	9	1.00		549	14	1.00	
70–79	391	14	1.42	0.72, 2.79	213	7	1.80	0.66, 4.91	178	7	1.17	0.47, 2.94
60–69	219	15	2.42	1.22, 4.80	105	5	2.10	0.68, 6.47	114	10	2.63	1.12, 6.14
<60	209	31	5.17	2.81, 9.50	106	12	4.70	1.88, 11.7	103	19	5.55	2.60, 11.8
<i>p</i> for trend§			<0.0001				0.001				<0.0001	
<i>p</i> for interaction¶							0.62					
% predicted FVC†												
≥80	1,364	41	1.00		684	18	1.00		680	23	1.00	
70–79	317	23	1.85	1.09, 3.16	153	7	1.58	0.64, 3.93	164	16	2.01	1.03, 3.92
60–69	124	12	2.47	1.24, 4.93	70	7	2.94	1.20, 7.23	54	5	1.96	0.70, 5.51
<60	78	7	2.35	0.99, 5.56	32	1	0.81	0.10, 6.34	46	6	3.50	1.31, 9.39
<i>p</i> for trend§			0.003				0.14				0.01	
<i>p</i> for interaction¶							0.64					
FEV ₁ :FVC ratio												
≥80	363	4	1.00		173	1	1.00		190	3	1.00	
70–79	928	25	2.20	0.76, 6.41	484	11	2.99	0.38, 23.4	444	14	1.90	0.54, 6.72
60–69	420	28	4.32	1.46, 12.8	199	12	6.47	0.82, 51.4	221	16	3.56	1.01, 12.6
<60	172	26	9.87	3.23, 30.1	83	9	9.98	1.22, 81.8	89	17	10.49	2.90, 37.9
<i>p</i> for trend§			<0.0001				0.001				<0.0001	
<i>p</i> for interaction¶							0.54					

* Excludes 2,177 participants: 206 who were missing valid data on baseline spirometry measures, 978 with a profusion rating greater than 0/1, 830 who were eligible on the basis of radiographic findings only, 133 never smokers, 20 who did not meet the asbestos eligibility criteria, eight with missing data on pack-years of smoking, and two who did not have a baseline radiograph.

† LC, lung cancer; RR, relative risk; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

‡ Risk estimate from a Cox regression model with stratification by cohort and study center and inclusion of the following covariates: age (<55, 55–64, or ≥65 years), years since quitting smoking (current smoking or 0–4, 5–9, 10–14, or >14 years), pack-years of smoking (<40, 40–60, or >60), trade (eight specified high-risk trades and an “other” category), intervention arm (active vitamins or placebo), years of working in a high-risk trade (<10, 11–20, 21–30, 32–40, or >40), presence of pleural abnormality (yes/no), and years since last asbestos exposure (0, 1–5, 6–10, 11–15, or >15).

§ Test for trend using a grouped linear variable.

¶ Test of interaction for intervention arm assignment × predictor of interest coded as a grouped linear variable.

in situ for epidemiologic research, we believe that the breadth of the sample and the completeness of its characterization justify these analyses, which were envisioned at the study's inception, as long as comparisons with any external population are avoided. Still, our findings must be viewed in light of the strengths and limitations of our study design. A strength is that the participants were identified and enrolled in the study prior to development of lung cancer. Although they are not necessarily representative of all occupationally exposed men, the asbestos-exposed cohort in CARET is very diverse and typical of many persons who seek clinical evaluation because of their exposure. Clinical characterization at baseline was standardized, including consistent interpretations of occupational and smoking histories, radiographs, and lung function. Although almost 15 percent of those enrolled in the study discontinued active vitamin use during the course of the study, very few subjects refused to participate in the aggressive follow-up effort; thus, ascertainment of lung cancer in this cohort was almost complete. Further-

more, the rules governing endpoint assessment assured a very high degree of precision regarding diagnosis (39, 40) in comparison with death certificates or the case ascertainment methods used in previous cohort studies (1–12).

However, these data were not without limitations. Almost 80 percent of the participants in this study had been exposed to asbestos in shipbuilding or other construction-related trades; manufacturing and other exposure settings were proportionally underrepresented. The diversity of exposures and workplaces limited our ability to quantify exposure beyond the crude surrogate measure used in the analysis—years of employment in a high-risk trade. Although several attempts have been made in the literature to provide semi-quantitative adjustment factors differentiating trades by levels of exposure (43), none was incorporated here, nor was there any information consistently available that would have allowed better exposure classification. Another limitation is that the radiographs were not read by a single panel but rather interpreted by separate B-readers at each study site.

The results of the small study undertaken to assess inter-reader agreement (41) revealed some differential classification of the radiographs, though generally by only one minor category. Finally, as with all randomized prospective trials, study participants cannot, as a group, be unthinkingly compared with other comparable men at risk. CARET participants were volunteers in a long-term study involving daily ingestion of potentially toxic vitamins, uncertainty regarding treatment arm, and the need to submit to regular examinations and follow-up surveys. By virtue of these selection effects, such volunteers may well be healthier than comparable men in the general population; or, alternatively, they may be more worried because of unmeasured factors. For this reason, all comparisons were internal, that is, made between various subgroups within the study, including the larger heavy-smoker cohort not exposed to asbestos. We made no comparisons with any external population. Likewise, generalization of our results to women, men with lesser amounts of asbestos exposure, or lifetime nonsmokers cannot be inferred from our data.

These limitations notwithstanding, certain conclusions can be drawn. We have confirmed previous observations that heavy asbestos exposure causes lung cancer in male smokers with asbestosis and that severity of asbestosis is a strong predictor of risk. The observation of synergy between asbestosis stage and study vitamins is new and provocative but remains as yet unconfirmed and unexplained mechanistically. The finding of increased lung cancer risk among men *without* radiographic evidence of fibrosis is noteworthy, but we cannot resolve the issue of whether this is a primary effect of asbestos or is due to asbestosis developing in the absence of any radiographic findings (44). Hence, we can neither affirm nor refute the contention (33–35) that asbestosis obligatorily mediates the relation between exposure and cancer, although the absence of any interaction with intervention arm in this subcohort may suggest a different carcinogenic pathway.

Regardless of whether that speculation withstands further scrutiny, we have provided new evidence that risk of lung cancer is increased in men with ILO-negative radiographs and that the risk rises steeply with years of exposure, contrary to the assertion of Wilkinson et al. (29). Our finding also supports the earlier observation of Hillerdal and Henderson (26) that the presence of pleural plaques on radiograph appears to almost double the risk, contrary to the impression of Partanen et al. (27) and the inference of Edelman (28). We offer no specific hypothesis for this, other than the likelihood that persons with plaques had more exposure on average than those without them. We also confirmed that obstructive lung dysfunction is a strong independent cancer predictor in this population. Neither residual confounding by tobacco use nor the possibility of differential proportions of subclinical asbestosis in these higher-risk subgroups appears to explain the observations.

Impossible to entirely exclude as contributory to these risk factors are the effects of completely unmeasured exposures, such as welding fumes, diesel exhaust, silica, nickel, hexavalent chromium, or other carcinogens to which construction and shipyard workers are exposed, and to whom higher doses might have accrued among those with more years of

working in the asbestos trades (45). However, such exposures would be unlikely to explain the steep and stepwise dose-response relations observed, since the associations between these exposures and lung cancer have been of generally low relative risk and exposures within our population diverged from trade to trade and work setting to work setting (e.g., general construction vs. shipbuilding).

In conclusion, we found that among current and former smokers exposed occupationally to asbestos, risk of lung cancer increases with increased exposure duration, even in persons without clinical evidence of asbestosis. Men with radiographically apparent pleural plaques and preexisting obstructive lung disease are at higher risk than men without them. Whether it is related to the apparently vitamin-sensitive effect observed in subjects with asbestosis or an independent effect of asbestos, intense occupational exposure, even in the absence of asbestosis, confers significant lung cancer risk in this population.

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