



Original Contribution

Evidence for Excess Colorectal Cancer Incidence among Asbestos-exposed Men in the Beta-Carotene and Retinol Efficacy Trial

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Received for publication September 29, 2004; accepted for publication June 1, 2005.

The relation between asbestos exposure and colorectal cancer remains controversial. The authors of this 1984–2004 US study examined the association among 3,897 occupationally exposed participants in the Beta-Carotene and Retinol Efficacy Trial (CARET) for chemoprevention of lung cancer, followed prospectively for 10–18 years. When a Cox stratified proportional hazards model was used, risks of colorectal cancer were elevated among male heavy smokers exposed to asbestos. Their relative risk was 1.36 (95% confidence interval: 0.96, 1.93) when compared with that for CARET heavy smokers not exposed to asbestos, after adjusting for age, smoking history, and intervention arm. The presence of asbestos-induced pleural plaques at baseline was associated with a relative risk of 1.54 (95% confidence interval: 0.99, 2.40); colorectal cancer risk also increased with worsening pulmonary asbestosis ($p = 0.03$ for trend). A dose-response trend based on years of asbestos exposure was less evident. Nonetheless, these data suggest that colorectal cancer risk is elevated among men occupationally exposed to asbestos, especially those with evidence of nonmalignant asbestos-associated radiographic changes.

asbestos; asbestosis; colorectal neoplasms; environmental exposure; prospective studies; randomized controlled trials; smoking

Abbreviations: CARET, Beta-Carotene and Retinol Efficacy Trial; CI, confidence interval.

In contrast to the findings for lung cancer, the relation between asbestos exposure and the risk of colorectal cancer is not universally accepted (1). Selikoff et al. (2) reported in 1964 a threefold excess mortality from colorectal cancer

among asbestos insulators. Excess deaths due to colorectal cancer were also found in their larger study of insulation workers in 1979 (3). Subsequent epidemiologic studies have yielded conflicting results. Early cohort studies from Italy

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(4), Norway (5), and the United States (6, 7) were positive. More recently, Albin et al. (8) reported a strong relation between colorectal cancer risk and cumulative asbestos dose but no overall excess of colorectal cancer. Other positive cohort studies include those by Jakobsson et al. (9), Raffin et al. (10), and Szeszenia-Dabrowska et al. (11). Scandinavian and US case-control studies have also observed significant increases in asbestos-associated odds ratios (12–16). In a meta-analysis by Homa et al. (17) using published reports of 20 amphibole asbestos-exposed cohorts, there was an elevated summary standardized mortality ratio (1.47, 95 percent confidence interval (CI): 1.09, 2.00).

Other investigators have not found an association. In a study of British asbestos workers, Hodgson et al. (18) found a significant deficit of colon cancer mortality (standardized mortality ratio = 54); Gardner et al. (19) found the expected rate. Multiple cohort studies found no association (20–27). In a meta-analysis of 69 occupational cohorts, Goodman et al. (28) concluded that data for gastrointestinal cancers showed no evidence of a significant association with asbestos exposure and no dose-response effect.

Proponents of an association have suggested that increased risk occurs as a local response to inhaled asbestos fibers cleared from the lung and swallowed, eventually penetrating the gastrointestinal mucosa and initiating tumor formation (29). Ehrlich et al. (30) reported the presence of asbestos bodies in the colon of an insulation worker with asbestosis and adenocarcinoma. Goldsmith (31), meanwhile, suggested that asbestos might act as a systemic carcinogen, noting that excess cancer at gastrointestinal sites parallels excess risk at other extrapulmonary sites. In any event, it is unclear whether synergism occurs with tobacco smoke, as for lung cancer, or putative dietary or other risk factors for colorectal cancer.

We previously analyzed colorectal cancer incidence among the asbestos-exposed males followed prospectively as part of the Beta-Carotene and Retinol Efficacy Trial (CARET), a multicenter, randomized, double-blinded, placebo-controlled chemoprevention trial designed to assess the effect of daily pharmacologic doses of vitamin A and beta-carotene on lung cancer incidence and mortality (32). Although the intervention was discontinued in 1996, 21 months ahead of schedule, when we recognized that the vitamins were associated with increased risk of lung cancer and increased total mortality (33, 34), CARET participants continue to be followed. Notably, the intervention had no measurable effect on colorectal cancer incidence or mortality (33).

MATERIALS AND METHODS

Study participants

For 10–18 years, the CARET trial for chemoprevention of lung cancer has followed 4,060 men occupationally exposed to asbestos as well as 14,254 heavy smokers (7,965 men and 6,289 women). The recruitment, enrollment, randomization, follow-up, and initial evaluations of the participants have been described in detail previously (32–37).

Two major cohorts were recruited at six centers in the United States: an asbestos-exposed cohort and a heavy-smoker cohort (figure 1). Participants for the asbestos-exposed cohort were recruited at five centers, four of which had large occupational health clinics. Subjects were referred by occupational and pulmonary physicians as well as by employers, unions, or lawyers or in response to public advertisements. Men were eligible for enrollment into the asbestos-exposed cohort during 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 been exposed to asbestos as documented by the following criteria: 1) they had worked in one of eight CARET-specified high-risk trades with established, regular asbestos exposure (insulation, sheet metal, plumbing, plasterboard, ship fitting, ship electrical work, boiler making, or ship scaling) for at least 5 years, starting at least 15 years previously; or 2) they had a history of occupational asbestos exposure in any job or occupation *and* had evidence of chest radiograph changes—pleural abnormalities or pulmonary fibrosis—consistent with a diagnosis of nonmalignant asbestos-related disease. In all, 3,244 men were enrolled as a result of these recruitment efforts. We added 816 men who had been enrolled previously in the pilot phase only in Seattle, Washington, using similar criteria except for a wider age span of 45–74 years and no smoking requirement (32), for a total of 4,060 men. Thirty-four percent of this asbestos-exposed cohort qualified by virtue of work history alone, 21 percent qualified by radiographic criteria alone, and 44 percent met both criteria. Excluded subsequently were 20 participants later found to be ineligible, eight whose smoking status was unknown, two whose radiographs were missing, and 133 from the pilot study who were lifelong nonsmokers, leaving data on 3,897 participants available for these analyses.

Because of the diversity of the asbestos exposure settings among the men in the asbestos-exposed cohort in construction, shipbuilding, and manufacturing and the fact that most exposure occurred long before study entry, no formal effort was undertaken to further classify participants by exposure dose, fiber type, or distribution of fiber sizes. Duration of exposure and severity of radiographic changes were used as crude surrogates of exposure dose instead, since all had postero-anterior and lateral chest radiographs before random assignment (37). Radiographic changes were independently assessed at each center by a B-reader, a radiologist, or a chest physician trained and certified in using the system of the National Institute for Occupational Safety and Health. International Labour Organization standard (1980) films were used to assess for each of two independent patterns of radiographic change typical of asbestos. Pleural reaction—bilateral thickening or plaque, with or without calcification—was rated as present or absent. Profusion throughout the lung fields of small irregular shadows was separately rated on a progressive 12-point scale: 0/–, 0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, 3/+, where the first number represents the major category and the second a modifier akin to plus or minus for letter grades. Category 1/0 changes and higher, typical for pulmonary asbestosis, were found in 39 percent of the participants at baseline; 47 percent had asbestos-associated pleural abnormalities.

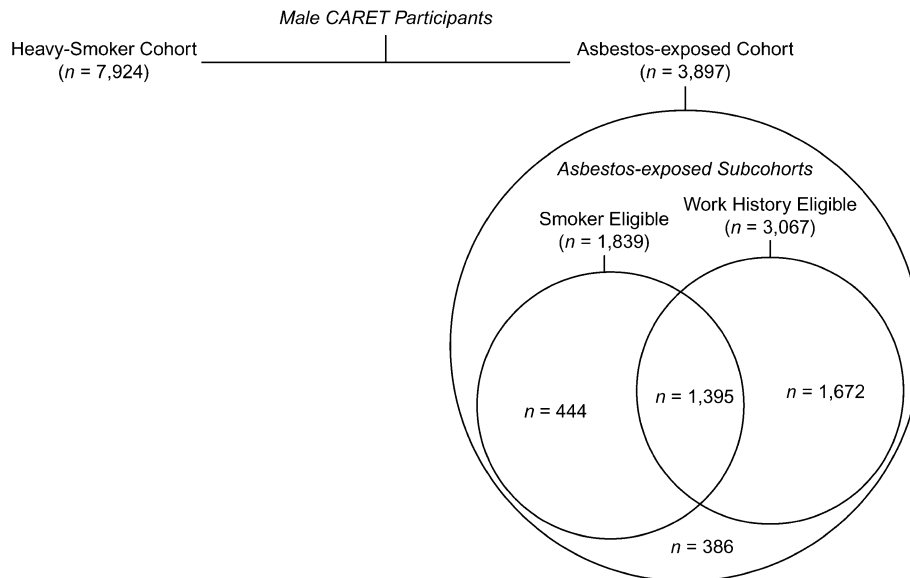


FIGURE 1. Major cohorts of male participants enrolled in the Beta-Carotene and Retinol Efficacy Trial (CARET) (Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004) and subcohorts within the asbestos-exposed cohort. The smoker-eligible subcohort ($n = 1,839$) consisted of members of the asbestos-exposed cohort who also met separate age and smoking criteria for inclusion in the heavy-smoker cohort of the CARET study. The work-history-eligible subcohort ($n = 3,067$) included men in the asbestos-exposed cohort who met the entrance criteria for >5 years of work in a designated high-asbestos-exposure trade; excluded were 830 men who worked in different occupations and qualified on the basis of chest radiographic findings at study entry. Of the 3,897 participants in the asbestos-exposed cohort, 1,395 qualified for both subcohorts; 386 were eligible for neither.

The heavy-smoker cohort of CARET was recruited simultaneously at three of the centers from managed-care organizations and health insurance rolls. Eligibility criteria were age 50–69 years at study entry, current or recent former smoking status (quit within the previous 6 years), and a history of 20 or more pack-years of cumulative smoking. Altogether, 7,965 men qualified for this cohort initially. Twenty-nine members of the heavy-smoker cohort with asbestos exposure histories sufficient to have been eligible for the asbestos-exposed cohort were subsequently excluded. An additional 12 male heavy smokers were found not to meet the heavy-smoker eligibility criteria and were excluded, leaving data on 7,924 male heavy smokers for analysis.

To exploit internal comparisons, the 3,897 asbestos-exposed cohort participants were further categorized by smoking status and eligibility criteria into two subcohorts (figure 1). The smoker-eligible subcohort included the 1,839 asbestos-exposed men who, in addition to asbestos-exposure criteria, also met the more rigorous smoking and age criteria for eligibility in the heavy-smoker cohort of CARET. The remaining 2,058 asbestos-exposed men who smoked for less than 20 pack-years, quit more than 6 years before, or were younger than age 50 years at randomization were excluded from this subcohort. To study work history as a risk factor, a second subcohort of 3,067 men was designated the work-history-eligible subcohort. These participants met the formal occupational exposure criterion for entry, that is, working for more than 5 years in one of the designated high-risk

trades beginning more than 15 years prior to randomization; 830 men exposed otherwise, who were enrolled based on asbestos-related radiographic changes on baseline examination, were excluded from this subcohort because their exposure histories were too diverse to classify. A total of 1,395 of the asbestos-exposed participants were members of each of these two subcohorts; 386 were eligible for neither.

Before initial evaluation, all participants signed consent forms that were reviewed by the human subjects protection committee.

Follow-up

Before the active intervention was discontinued in January 1996, participants were contacted by the local study center three times per year and were evaluated in person at least once. After active intervention was stopped, contact was reduced to an annual phone call until April 2000. Since then, all follow-up has been conducted annually by mail and phone by the CARET Coordinating Center in Seattle. At each contact, participants were asked whether they had been diagnosed with cancer since the previous contact. Because this diagnosis was not the primary focus of the study, colorectal cancer cases did not receive the same degree of scrutiny as lung cancer cases. Detection of colorectal cancer was by participants' report. There was no review of tissue histology or staging information, but the endpoints committee reviewed medical records, including pathology reports.

This paper includes complete follow-up information through December 2003.

Statistical analysis

To examine the relation between asbestos exposure and colorectal cancer incidence, the following analyses were performed: 1) comparison of the colorectal cancer risk for the smoker-eligible subcohort of the asbestos-exposed cohort with that for the heavy-smoker cohort, using radiographic changes as crude surrogates for asbestos exposure dose; 2) comparison of risk within the asbestos-exposed cohort, using radiographic changes as surrogates for exposure dose; 3) comparison of risk within the work-history-eligible subcohort, using years working in a high-risk trade, years since first exposure to asbestos, and specific trade as surrogates for exposure dose; and 4) survival analysis postdiagnosis comparing colorectal cancer cases in the smoker-eligible subcohort with cases in the heavy-smoker cohort.

Stratified Cox proportional hazards models were used to obtain colorectal cancer relative risk estimates and 95 percent confidence intervals. All models were stratified on enrollment period (pilot phase vs. full study). Models included adjustment for age (as a linear variable), baseline smoking status (current, former), pack-years of smoking (≤ 40 , 41–60, > 60), and intervention assignment (vitamin A + beta-carotene, placebo). Comparisons restricted to the asbestos-exposed workers were further stratified on enrollment center and included additional adjustment for years since quitting smoking. Only two of the six CARET study centers recruited participants for both the asbestos and heavy-smoker cohorts. Thus, in the comparison between the asbestos-exposed smoker-eligible subcohort and the non-asbestos-exposed heavy-smoker cohort, study center could not be evaluated as a potential confounder. Adjustment for body mass index and dietary intake of calcium, fiber, fat, and percentage of energy from fat as potential confounders had little effect, so they were excluded from the final models.

Radiographic findings (presence of pleural reaction, International Labour Organization profusion score) and work history (years working in a high-risk trade, years since first exposure, specific trade) were examined independently as surrogates of asbestos exposure. Radiographic variables were fit simultaneously in models including the asbestos-exposed cohort and its subcohorts only; to avoid overfitting bias, no adjustment for years working in a high-risk trade was made in these analyses. A similar approach was used to examine the association between asbestos-related work history measures and colorectal cancer incidence among the work-history-eligible subcohort. Participants eligible on the basis of radiographic findings only were excluded from this analysis to avoid bias due to a potential underreporting of years of exposure in this subgroup. In this paper, results of this analysis are presented both unadjusted for specific trade—to assess possible differences by trade in the intensity of asbestos exposure per year—and adjusted, assuming that variation may reflect nonasbestos, trade-specific exposures.

For the comparison to the heavy-smoker cohort, the asbestos-related variables were assessed in separate models,

with the heavy-smoker cohort serving as the referent in each model. Likelihood ratio tests were performed to test for linear trend across categories and to test whether associations between asbestos-related measures and colorectal cancer risk were modified by age, smoking status, pack-years of smoking, and intervention assignment. No test of interaction was statistically significant. Kaplan-Meier estimates were calculated to examine postdiagnosis survival by risk population; log-rank tests were performed on differences in survival curves. All significance tests were two sided. For our analyses, we used SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

There were 85 incident cases of colorectal cancer observed among the 3,897 participants in the asbestos-exposed cohort. Among the 7,924 men in the heavy-smoker cohort, there were 123. Crude incidence rates and 95 percent confidence intervals for colorectal cancer in the asbestos-exposed and heavy-smoker cohorts were, respectively, 2.0 (95 percent CI: 1.6, 2.5) and 1.6 (95 percent CI: 1.3, 1.9) per 1,000 person-years. Incidence rates did not differ by intervention arm overall or within each cohort. The crude incidence rates for the smoker-eligible and work-history-eligible subcohorts of the asbestos-exposed cohort were 2.2 (95 percent CI: 1.6, 3.0) and 2.1 (95 percent CI: 1.6, 2.6), respectively. Demographic, smoking, occupational, and dietary histories for the asbestos-exposed and heavy-smoker cohorts are presented in table 1. All parameters except asbestos exposure and smoking were similar. The same parameters for the smoker-eligible and work-history-eligible subcohorts are shown in table 2. Work-history-eligible participants spent a higher average number of years working in high-risk trades but had similar durations of exposure to asbestos overall.

Since no appropriate external comparison group for these volunteer study participants was available, we used the CARET heavy-smoker cohort as a non-asbestos-exposed comparison group for the asbestos-exposed cohort and its smoker-eligible subcohort. Tests for homogeneity revealed that the heavy-smoker cohort and smoker-eligible subcohort were indistinguishable regarding all measurable factors except asbestos; although some heavy smokers had short-duration asbestos exposures (table 1), almost none was working in high-risk trades after age 29 years, who would have qualified as asbestos exposed, so these heavy smokers were excluded (refer to the Materials and Methods section). Table 3 shows the crude incidence rates and results of the adjusted analyses for the asbestos-exposed smoker-eligible subcohort versus the unexposed heavy-smoker cohort. When we adjusted for smoking history, age, and intervention arm, the asbestos-exposed smoker-eligible subcohort had a 36 percent higher rate of colorectal cancer compared with the heavy-smoker cohort, although it was not statistically significant (95 percent CI: 0.96, 1.93). Asbestos-exposed participants in the smoker-eligible subcohort who had pleural abnormalities had a 54 percent increased risk of colorectal cancer compared with participants in the heavy-smoker cohort ($p = 0.05$). There was also a significant trend

TABLE 1. Demographics of the asbestos-exposed cohort and the male heavy-smoker cohort, Beta-Carotene and Retinol Efficacy Trial: Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004*

| Variable | Asbestos-exposed cohort† | | | | | | Heavy-smoker cohort‡ | | | | | |
|--|--------------------------|-------|----|-------------------------|-----|----|----------------------|-------|----|-------------------------|-----|----|
| | Total | | | Colorectal cancer cases | | | Total | | | Colorectal cancer cases | | |
| | Mean (SD§) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % |
| No. of participants | | 3,897 | | | 85 | | | 7,924 | | | 123 | |
| Age (years) | 57 (7) | | | 61 (6) | | | 58 (5) | | | 60 (5) | | |
| <55 | | 1,585 | 41 | | 15 | 18 | | 2,557 | 32 | | 25 | 20 |
| 55–64 | | 1,616 | 41 | | 40 | 47 | | 4,150 | 52 | | 65 | 53 |
| ≥65 | | 696 | 18 | | 30 | 35 | | 1,217 | 15 | | 33 | 27 |
| Smoking status at enrollment | | | | | | | | | | | | |
| Current | | 1,548 | 40 | | 29 | 34 | | 5,134 | 65 | | 80 | 65 |
| Former | | 2,349 | 60 | | 56 | 66 | | 2,790 | 35 | | 43 | 35 |
| Years since quitting smoking (no.) (former smokers) | | | | | | | | | | | | |
| 0–4 | | 636 | 27 | | 13 | 23 | | 2,020 | 72 | | 27 | 63 |
| 5–6 | | 365 | 16 | | 5 | 9 | | 770 | 28 | | 16 | 37 |
| 7–9 | | 351 | 15 | | 11 | 20 | | | | | | |
| 10–14 | | 595 | 25 | | 17 | 30 | | | | | | |
| >14 | | 402 | 17 | | 10 | 18 | | | | | | |
| Pack-years of smoking (no.) | 43 (24) | | | 46 (25) | | | 53 (22) | | | 55 (22) | | |
| ≤40 | | 2,051 | 53 | | 43 | 51 | | 2,522 | 32 | | 35 | 28 |
| 41–60 | | 1,127 | 29 | | 23 | 27 | | 3,013 | 38 | | 48 | 39 |
| >60 | | 719 | 18 | | 19 | 21 | | 2,386 | 30 | | 40 | 33 |
| Years of asbestos exposure (no.) | 27 (10) | | | 28 (10) | | | 3 (9) | | | 2 (6) | | |
| Years working in a high-risk trade (no.) | 19 (13) | | | 21 (13) | | | <1 (<1) | | | <1 (<1) | | |
| Body mass index (kg/m ²) | 28.8 (4.6) | | | 29.7 (4.2) | | | 27.9 (4.6) | | | 27.2 (4.1) | | |
| Calcium intake (mg/day) | 814 (492) | | | 790 (470) | | | 775 (445) | | | 832 (493) | | |
| Fat intake (g/day) | 84 (38) | | | 81 (40) | | | 79 (35) | | | 85 (39) | | |
| Energy from fat (%) | 38 (7) | | | 38 (8) | | | 38 (8) | | | 38 (8) | | |
| Fiber intake (g/day) | 16 (7) | | | 16 (7) | | | 15 (7) | | | 16 (7) | | |

* Some percentages do not total 100 because of rounding.

† Excludes 163 asbestos-exposed participants: 133 never smokers, 20 not meeting the asbestos eligibility criteria, eight for whom number of pack-years was unknown, and two who did not have a baseline radiograph.

‡ Restricted to male heavy smokers, excluding 41 participants: 12 who did not meet the heavy-smoker eligibility criteria and 29 who met the eligibility criteria for the asbestos-exposed cohort.

§ SD, standard deviation.

in the risk of colorectal cancer with increasing profusion score on radiograph ($p = 0.03$ for trend). On the other hand, postdiagnosis survival of cases in the two groups was similar (figure 2).

Assuming that the presence of pleural changes and the severity of radiograph profusion score are biologic markers for asbestos exposure dose, these findings are consistent with a dose-response relation between asbestos exposure and the risk of colorectal cancer. Because this comparison provided the strongest evidence for an association between asbestos and colon cancer risk, we looked for possible residual confounding by assessing the effect of smoking on colorectal cancer risk, controlling for asbestos exposure, by using a model that included baseline risk population

(asbestos vs. heavy smoker), age, and intervention arm. The risk estimate for current ($n = 6,239$) versus former ($n = 3,524$) smoking was associated with a relative risk of 1.05 for colon cancer (95 percent CI: 0.77, 1.45). Heavier smokers (41–60 pack-years, $n = 3,694$) had a relative risk of 0.87 (95 percent CI: 0.59, 1.27) compared with those smoking for less than or equal to 40 pack-years ($n = 3,140$). The 2,929 smokers with more than 60 pack-years of smoking had a relative risk of 0.97 (95 percent CI: 0.65, 1.44).

Table 4 shows the relation between radiographic changes and colon cancer risk within the entire asbestos-exposed cohort. The pattern of increasing relative risk with increasing abnormality, when asbestos-exposed participants with a normal radiograph were used as the comparison group,

TABLE 2. Demographics of the asbestos-exposed smoker-eligible subcohort and the work-history-eligible subcohort, Beta-Carotene and Retinol Efficacy Trial: Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004*

| Variable | Smoker-eligible subcohort† (asbestos exposed) | | | | | | Work-history-eligible subcohort‡ (asbestos exposed) | | | | | |
|--|---|-----|---|-------------------------|-----|---|---|-----|---|-------------------------|-----|---|
| | Total | | | Colorectal cancer cases | | | Total | | | Colorectal cancer cases | | |
| | Mean (SD)§ | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % | Mean (SD) | No. | % |
| No. of participants | 1,839 | | | 42 | | | 3,067 | | | 71 | | |
| Age (years) | 59 (6) | | | 62 (4) | | | 56 (7) | | | 61 (7) | | |
| <55 | 531 29 | | | 4 10 | | | 1,360 44 | | | 13 18 | | |
| 55–64 | 980 53 | | | 23 55 | | | 1,205 39 | | | 30 42 | | |
| ≥65 | 328 18 | | | 15 36 | | | 502 16 | | | 28 39 | | |
| Smoking status at enrollment | | | | | | | | | | | | |
| Current | 1,105 60 | | | 24 57 | | | 1,235 40 | | | 24 34 | | |
| Former | 734 40 | | | 18 43 | | | 1,832 60 | | | 47 66 | | |
| Years since quitting smoking (no.) (former smokers) | | | | | | | | | | | | |
| 0–4 | 476 65 | | | 13 72 | | | 480 26 | | | 10 21 | | |
| 5–6 | 258 35 | | | 5 28 | | | 274 15 | | | 4 9 | | |
| 7–9 | | | | | | | 281 15 | | | 10 21 | | |
| 10–14 | | | | | | | 468 26 | | | 16 34 | | |
| >14 | | | | | | | 329 18 | | | 7 15 | | |
| Pack-years of smoking (no.) | 53 (23) | | | 55 (29) | | | 42 (24) | | | 46 (24) | | |
| ≤40 | 618 34 | | | 15 36 | | | 1,652 54 | | | 35 49 | | |
| 41–60 | 678 37 | | | 12 29 | | | 874 28 | | | 20 28 | | |
| >60 | 543 30 | | | 15 36 | | | 541 18 | | | 16 23 | | |
| Years of asbestos exposure (no.) | 28 (10) | | | 30 (9) | | | 27 (10) | | | 28 (10) | | |
| Years working in a high-risk trade (no.) | 19 (14) | | | 23 (14) | | | 24 (10) | | | 25 (11) | | |
| Body mass index (kg/m ²) | 28.3 (4.8) | | | 29.9 (3.5) | | | 28.7 (4.6) | | | 29.6 (4.1) | | |
| Calcium intake (mg/day) | 790 (478) | | | 784 (534) | | | 810 (489) | | | 797 (502) | | |
| Fat intake (g/day) | 85 (38) | | | 82 (38) | | | 84 (38) | | | 81 (41) | | |
| Energy from fat (%) | 38 (8) | | | 39 (8) | | | 38 (8) | | | 38 (8) | | |
| Fiber intake (g/day) | 16 (7) | | | 16 (2) | | | 16 (7) | | | 15 (7) | | |

* Some percentages do not total 100 because of rounding.

† 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.

‡ Excludes 993 participants: 830 who were eligible on the basis of asbestos-related radiographic changes and did not meet the occupational exposure criterion, in addition to the 163 participants dropped previously (refer to table 1).

§ SD, standard deviation.

was similar to that shown in table 3 but did not achieve statistical significance.

As an alternative to radiographic change as a measure of dose, we looked at the effect of years of exposure in a high-risk trade, years since first exposure to asbestos, and specific trade on the risk of colorectal cancer among the work-history-eligible subcohort (eligible for the study based on a work history of 5 or more years in one of the jobs defined as high-risk trades). Table 5 shows the relative risks for colorectal cancer in this subcohort, adjusting for age, years since quitting smoking, pack-years of smoking, intervention arm, years working in a high-risk trade, and time since first asbestos exposure; models with and without adjustment

for trade are presented to explore the possibility of trade-specific heterogeneity. Although the trend for years in a high-risk trade was not statistically significant, more than 10 years in a high-risk trade carried a progressively increasing risk of colorectal cancer with increasing number of years of exposure up until 30 years; those participants with 21–30 years of exposure had a 74 percent increased risk compared with those with less than 10 years of exposure. After 30 years in a high-risk trade, the risk progressively decreased, those with more than 40 years of exposure having a risk lower than that for those with less than 10 years of exposure. Time since first asbestos exposure had no predictive effect on the risk of colorectal cancer. Although the numbers were

TABLE 3. Colorectal cancer incidence among asbestos-exposed participants in the smoker-eligible subcohort and the non-asbestos-exposed heavy-smoker cohort, Beta-Carotene and Retinol Efficacy Trial: Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004

| | Total no.* | Colorectal cancer cases (no.) | RR† | 95% CI†,‡ | p value |
|--|------------|-------------------------------|------|------------|---------|
| At-risk population | | | | | |
| Heavy-smoker cohort (non-asbestos-exposed) | 7,924 | 123 | 1.00 | | 0.09§ |
| Smoker-eligible subcohort (asbestos-exposed) | 1,839 | 42 | 1.36 | 0.96, 1.93 | |
| Pleural abnormality¶ | | | | | |
| Heavy-smoker cohort (non-asbestos-exposed) | 7,924 | 123 | 1.00 | | 0.17§ |
| Smoker-eligible pleura negative | 953 | 18 | 1.17 | 0.71, 1.92 | |
| Smoker-eligible pleura positive | 886 | 24 | 1.54 | 0.99, 2.40 | |
| Radiographic profusion rating category (major categories)# | | | | | |
| Heavy smoker | 7,924 | 123 | 1.00 | | 0.03** |
| 0/– to 0/1 | 1,007 | 20 | 1.20 | 0.75, 1.93 | |
| 1/0 to 1/2 | 769 | 19 | 1.44 | 0.89, 2.34 | |
| 2/1 to 2/3 | 47 | 2 | 2.47 | 0.61, 10.0 | |
| 3/2 to 3/+ | 16 | 1 | 3.92 | 0.54, 28.2 | |

* Excludes 2,221 asbestos 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.

† RR, relative risk; CI, confidence interval.

‡ Estimates from Cox proportional hazards model stratified on enrollment period (pilot or efficacy phase) and adjusted for age, smoking status at baseline (current, former), pack-years of smoking (≤ 40 , 41–60, > 60), and intervention arm.

§ Test for heterogeneity.

¶ Presence of bilateral pleural thickening or plaques on radiography, with or without calcification.

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

** Test for trend using group linear covariates.

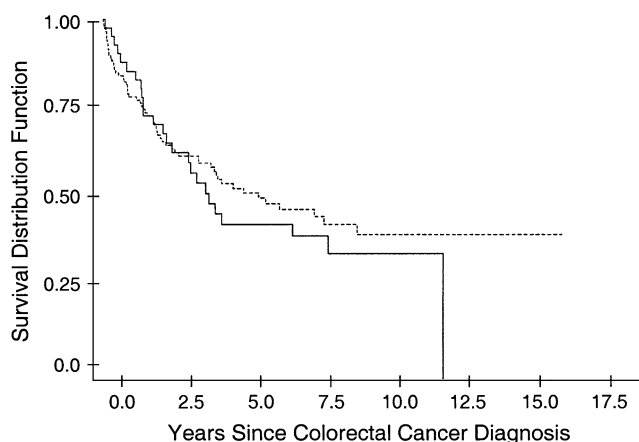


FIGURE 2. Postdiagnosis colorectal cancer survival in two sub-populations of the Beta-Carotene and Retinol Efficacy Trial (Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004). Cases in the asbestos-exposed smoker-eligible subcohort ($n = 42$, solid line) were compared with cases in the non-asbestos-exposed heavy-smoker cohort ($n = 123$, broken line).

small and confidence intervals were wide, there was a suggestion of possible trade-associated differences (table 5).

DISCUSSION

The results of this large, longitudinal cohort study suggest an increased risk of colorectal cancer among men with radiographic evidence of nonmalignant asbestos-related disease. This risk was most clearly observed when the (asbestos-exposed) smoker-eligible subcohort was compared with the (non-asbestos-exposed) heavy-smoker cohort (table 3). In this comparison, there appeared to be a dose-response relation when profusion score on chest radiograph was used as a surrogate for dose. We believe that this comparison is most appropriate because it controls for smoking and those unmeasured behaviors likely associated with heavy smoking. The dose trend, although similar, was not significant for the internal analysis of the whole asbestos-exposed cohort (table 4) when the same surrogates for exposure were used—radiographic changes—suggesting that the trend seen in table 3 was anchored by the large nonexposed comparison group. In each comparison, however, both the

TABLE 4. Radiographic predictors of colorectal cancer incidence among the asbestos-exposed cohort, Beta-Carotene and Retinol Efficacy Trial: Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004

| | Total no.* | Colorectal cancer cases (no.) | RR†,‡ | 95% CI† | p value |
|---|------------|-------------------------------|-------|------------|---------|
| Pleural abnormality§ | | | | | |
| Negative | 2,050 | 34 | 1.00 | | 0.15¶ |
| Positive | 1,847 | 51 | 1.40 | 0.88, 2.23 | |
| Radiographic profusion rating category# | | | | | |
| 0/– to 0/1 | 2,365 | 48 | 1.00 | | 0.49** |
| 1/0 to 1/2 | 1,424 | 33 | 1.12 | 0.70, 1.80 | |
| 2/1 to 2/3 | 84 | 3 | 1.41 | 0.42, 4.75 | |
| 3/2 to 3/+ | 24 | 1 | 1.38 | 0.18, 10.6 | |
| Radiographic abnormality | | | | | |
| Negative | 1,325 | 21 | 1.00 | | 0.45¶ |
| Parenchymal changes | 725 | 13 | 1.21 | 0.59, 2.48 | |
| Pleural abnormality | 1,040 | 27 | 1.47 | 0.81, 2.66 | |
| Parenchymal + pleural | 807 | 24 | 1.62 | 0.85, 3.09 | |

* Excludes 163 participants: 133 never smokers, 20 who did not meet the asbestos eligibility criteria, eight for whom information on pack-years was missing, and two who did not have a baseline radiograph.

† RR, relative risk; CI, confidence interval.

‡ Estimates were derived from a multivariate Cox proportional hazards model stratified on enrollment period (pilot or efficacy phase) and study center and included the following covariates: age, years since quitting smoking (current smokers, 0–4, 5–9, 10–14, >14), pack-years of smoking (≤ 40 , 41–60, >60), intervention arm (active vitamins, placebo), occupational trade (eight study-specific high-risk trades and an “other” category), presence of pleural abnormality, and profusion rating (<1/0, 1/0–1/2, 2/1–2/3, >2/3).

§ Presence of bilateral pleural thickening or plaques on radiography, with or without calcification.

¶ Test for heterogeneity.

Test for trend using group linear covariates.

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

presence of pleural plaques and the International Labour Organization profusion score appear to be predictive of colorectal cancer risk. Smoking is unlikely to confound this association because it had no independent effect on colorectal cancer risk.

Our results were less impressive when we used years working in a high-risk trade as surrogates of exposure (table 5). There are several possible reasons. For one, all participants in the work-history-eligible subcohort had significant exposure to asbestos because they worked in a high-risk trade for at least 5 years; even those we classified as least exposed by using the surrogate measures of exposure dose were heavily exposed compared with men in the heavy-smoker cohort, so the range of exposures is limited. A second possibility for the weaker association is that the use of years in a high-risk trade leads to substantially greater misclassification than using radiographic change as the exposure marker. Alternatively, the effect may be limited to those men exposed heavily enough to have radiographic changes or a differential susceptibility to asbestos effects manifested by the abnormal radiographs.

Another possibility for the observed results is that selective pressures have operated in the population. The analysis within the work-history-eligible subcohort revealed that

years in a high-risk trade predicted colorectal cancer risk up to 30, beyond which the colorectal cancer rate started to drop. This finding may be due to a survival effect, in which those most heavily exposed died preferentially of lung cancer, mesothelioma, or other diseases strongly associated with asbestos exposure. It may also indicate a healthy-worker effect, whereby those more physically active or whose body mass is lower—protective factors for colorectal cancer—remained in the trades for longer periods. That adjustment for body mass index did not alter the results weighs against such an interpretation.

Alternatively, it is possible that results of the comparison between the (asbestos-exposed) men in the smoker-eligible subcohort and those in the (non-asbestos-exposed) heavy-smoker cohort are spurious. Since smoking, unlike asbestos, is not a strongly suspected risk factor for colorectal cancer, there may be a greater tendency for health-care providers to more aggressively screen for colorectal cancer among asbestos-exposed workers, resulting in detection bias. In fact, many asbestos-exposed cohort participants had been advised to receive screening for colorectal cancer at occupational health clinics and through targeted educational programs. If there were differential detection of colorectal cancer between these two groups, however, we would expect

TABLE 5. Work-history predictors of colorectal cancer incidence in the asbestos-exposed work-history-eligible subcohort, Beta-Carotene and Retinol Efficacy Trial: Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004

| | Total* | Colorectal cancer cases (no.) | RR†,‡ | 95% CI† | p value | RR§ | 95% CI | p value |
|---|--------|-------------------------------|-------|------------|---------|------|------------|---------|
| Years working in a high-risk trade (no.) | | | | | | | | |
| <10 | 410 | 7 | 1.00 | | 0.4¶ | 1.00 | | 0.83¶ |
| 11–20 | 776 | 16 | 1.37 | 0.56, 3.36 | | 1.40 | 0.57, 3.45 | |
| 21–30 | 1,003 | 25 | 1.52 | 0.65, 3.56 | | 1.74 | 0.74, 4.10 | |
| 31–40 | 722 | 20 | 1.04 | 0.43, 2.54 | | 1.20 | 0.48, 2.99 | |
| >40 | 156 | 3 | 0.49 | 0.12, 2.00 | | 0.62 | 0.15, 2.54 | |
| Years since first asbestos exposure (no.) | | | | | | | | |
| 15–28 | 818 | 10 | 1.00 | | 0.71¶ | 1.00 | | 0.52¶ |
| 29–34 | 818 | 13 | 1.12 | 0.48, 2.59 | | 1.12 | 0.48, 2.60 | |
| 35–41 | 724 | 19 | 1.10 | 0.47, 2.57 | | 1.15 | 0.49, 2.71 | |
| >41 | 707 | 29 | 1.20 | 0.48, 3.04 | | 1.37 | 0.54, 3.48 | |
| Trade# | | | | | | | | |
| Plumber/pipe fitter | 955 | 15 | | | | 1.00 | | 0.08** |
| Shipyard boilermaker | 701 | 22 | | | | 1.82 | 0.93, 3.59 | |
| Sheet-metal worker | 564 | 10 | | | | 1.04 | 0.46, 2.34 | |
| Asbestos worker/insulator | 238 | 7 | | | | 2.16 | 0.87, 5.36 | |
| Shipfitter | 202 | 7 | | | | 2.28 | 0.92, 5.65 | |
| Shipyard electrician | 170 | 6 | | | | 2.27 | 0.85, 6.05 | |
| Plasterboard worker | 137 | 1 | | | | 0.51 | 0.07, 3.97 | |
| Ship scaler | 45 | 3 | | | | 3.84 | 1.05, 14.0 | |
| Other | 55 | 0 | | | | 0.00 | | |

* 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 for whom information on pack-years of smoking was missing, and two who did not have a baseline radiograph.

† RR, relative risk; CI, confidence interval.

‡ Estimates were derived from a multivariate Cox proportional hazards model stratified on enrollment period (pilot or efficacy phase) and study center and included the following covariates: age, years since quitting smoking (current smokers, 0–4, 5–9, 10–14, >14), pack-years of smoking (≤ 40 , 41–60, >60), intervention arm (active vitamins, placebo), years working in a high-risk trade (<10, 11–20, 21–30, 31–40, >40), and years since first asbestos exposure (15–28, 29–34, 35–41, >41).

§ From a model that also included primary trade.

¶ Test for trend using grouped linear covariates.

Test for heterogeneity.

** Plumber/pipe fitter, the most prevalent trade, was used as the reference group for all other trades.

the disease to have been detected at early stages in the asbestos-exposed subjects and that cancer survival would be improved relative to that for the heavy smokers. Since we did not have complete colorectal cancer staging information for the study participants, we assessed survival after diagnosis (figure 2). From this analysis it is evident that the asbestos cohort subjects are not surviving longer. Though unlikely, it is conceivable that results were confounded by differences among the participants in terms of unmeasured risk factors such as family history of colorectal cancer, recreational activity, or use of nonsteroidal anti-inflammatory drugs.

There are other potential limitations of this study. Unlike lung cancer, colorectal cancer was not the primary endpoint of the CARET study, so there was no review of the histopathologic diagnoses of the reported colorectal cancer cases. We did obtain medical record confirmation of the subjects'

reports; however, we cannot entirely exclude misclassification of mesothelioma or adenocarcinoma of other origin. Likewise, we cannot comment on the completeness of ascertainment of colorectal cancer among the participants, which, as we noted, might be different between the heavy-smoker and asbestos-exposed cohorts. We were also unable to exclude the effects of unmeasured occupational exposures of construction and shipyard workers, such as welding fumes, diesel exhaust, silica, nickel, hexavalent chromium, or other carcinogens, to which higher doses might have accrued among those with longer years of work (38). These unmeasured exposures, differences in exposure to asbestos per year of work, selection differences, or chance could account for the differences observed by trade (table 5).

We are additionally limited in our ability to generalize our results. CARET participants are volunteers with possibly unique selection-related characteristics. They may be

“healthier” than comparable subjects in the general population or, alternatively, more worried about their health. For this reason, all comparisons we made—even the “external” comparison with the heavy-smoker cohort—were “internal” to the CARET population. As such, our results should not be extrapolated uncritically to women, men with lower levels of exposure to asbestos, or nonsmokers.

Despite these limitations, this study has many important strengths. We were able to identify an appropriate comparison group with nominal exposure to asbestos. Participants were identified and enrolled in the study before they developed colorectal cancer. Characterization of participants at baseline was exhaustive and standardized, including consistent interpretations of the occupational and smoking histories and chest radiographs. The asbestos-exposed cohort of CARET is very diverse and likely representative of the many occupationally exposed men for whom the risk of colon cancer is a clinically relevant issue.

In conclusion, we have provided new evidence consistent with the hypothesis that asbestos exposure leads to increased risk of colorectal cancer. An apparent dose-response relation was observed for those men with radiographic changes, similar to that seen in this CARET population for lung cancer (39), although colorectal cancer occurs only about half as often. Unlike our lung cancer results, no clear effect was evident on colon cancer risk for those without pleural changes or asbestosis on radiograph, raising the question of whether chest radiographic findings reflect dose or host susceptibility to asbestos in both the lungs and the gastrointestinal tract. Neither selection bias nor residual confounding by diet or other risk factors appears to be a better explanation for our observations than a causal link, especially for those with asbestos-associated changes on radiograph who have also been heavy smokers. We conclude that, for such men, previous recommendations for colorectal cancer screening appear well founded.

ACKNOWLEDGMENTS

This study was supported by National Cancer Institute grant U01 CA63673.

Conflict of interest: none declared.

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