

# Brayton ♦ Purcell LLP

## TRIAL LAWYERS

ALAN R. BRAYTON  
GILBERT L. PURCELL

DAVID R. DONADIO  
CHRISTOPHER E. ANDREAS  
LLOYD F. LEROY

OF COUNSEL  
JEFFREY D. EISENBERG\*

\* ADMITTED ONLY IN STATES  
OTHER THAN CALIFORNIA

222 Rush Landing Road  
P O Box 6169  
Novato, California 94948-6169  
Telephone: (415) 898-1555  
Facsimile: (415) 898-1247

Portland: (503) 295-4931  
Los Angeles: (415) 898-1555  
Salt Lake City: (801) 366-9100

Email: [mail@braytonlaw.com](mailto:mail@braytonlaw.com)  
[www.braytonlaw.com](http://www.braytonlaw.com)

February 13, 2006

NICHOLAS ALOIA  
MARIE N. APPEL  
JARED J. BABULA  
LEAH F. BACCITICH  
DAVID H. BACKENSTOE  
LOUIS G. BEARY, Jr.  
NANCE F. BECKER  
BRYAN S. BORDON  
GARY L. BRAYTON  
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HUGH C. COOK  
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PETER B. FREDMAN  
CHRISTINA D. FRENCH  
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KERRY LAIW  
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KIMBERLY A. WILLIAMS  
NANCY T. WILLIAMS  
DEBORAH C. YANG  
STEVEN W. YUEN

## VIA FACSIMILE, U.S. MAIL & ELECTRONIC-MAIL

Senator Tom Coburn  
172 Russell Senate Office Building  
Washington, D.C. 20510

Facsimile (202) 224-6008

Senator Tom Coburn  
100 North Broadway, Ste. 1820  
Oklahoma City, OK 73102

Facsimile (405) 231-5051

Re: S. 852 - Asbestos Legislation

Dear Senator Coburn:

I was dismayed to hear your remarks on the Senate Floor last week (February 9, 2006) to the effect that “no science supports any association between colorectal cancer and asbestos exposure.”

Your statement is incorrect. It needs to be corrected.

The Environmental Protection Agency (“EPA”), after evaluation of the medical and scientific literature, agrees there is indeed a causal connection between asbestos exposure and colorectal cancer. See attached copy of the Federal Register, 40 CFR Part 763, Environmental Protection Agency, Asbestos Final Rule, July 12, 1989, Volume 54, No. 132, p.29469, which states:

“...after weighing available information, EPA believes that there is evidence of a strong causal relationship between asbestos exposure and gastrointestinal cancer excess.”

Moreover, a recent comprehensive study published last September in the American Journal of Epidemiology, co-authored by well-recognized national and world-leading researchers and doctors in the study of asbestos-related disease including, inter alia, Dr. Oluremi Aliyu and Dr. Mark Cullen of Yale University School of Medicine, Dr. John Balmes of UC Berkeley, Dr. Linda Rosenstock<sup>1</sup>, M.P.H., of UCLA, and Dr. Carl Brodtkin, one of the panel members involved in the American Thoracic Society 2004 blue-ribbon committee authoring the current clinical criteria for diagnosing asbestos-related disease, concluded:

“ . . . asbestos exposure leads to increased risk of colorectal cancer.” (Emphasis added.)

See: Aliyu, O.A., et al., “Evidence for Excess Colorectal Cancer Incidence Among Asbestos-Exposed Men in the Beta-Carotene and Retinol Efficacy Trial,” Am. J Epidemiology, Vol. 162, No. 9 (2005). (Copy enclosed for convenience.)

Enclosed please find a copy of a medical report from Dr. Irwin Stoloff, a well-respected contemporary of Dr. Irving Selikoff, who makes the causal association in a man exposed to asbestos in shipyards and as a treatment plant engineer. After reviewing the medical records, and citing at least five references to the medical literature, Dr. Stoloff writes:

“Asbestos fiber exposure is a known risk factor for colorectal cancer.... Asbestos is a causative factor in Mr. Pierce’s colorectal cancer.” (See page 3.)

To be sure, not all researchers agree on the point. Nevertheless, your statement on the Senate Floor and in the Record was incorrect and should be corrected.

Although I presently live in California, I am from Norman, Oklahoma and went to the University of Oklahoma “University School” for elementary and junior high. My mother still lives in Blanchard and is active in the surrounding communities. I have many relatives there who are your constituents, all of whom oppose this corporate bailout legislation.

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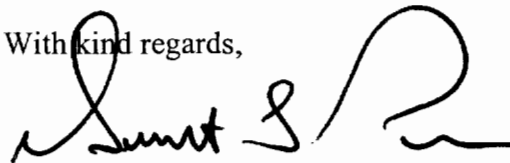
<sup>1</sup>Dr. Rosenstock is former Director of (NIOSH) National Institute for Occupational Safety and Health. Her “Textbook of Clinical Occupational and Environmental Medicine,” in the section on colorectal cancer, states:

“ . . . few workplace exposures have been consistently linked with cancer of the lower GI tract. One exception is asbestos. Frumkin and Berlin (1988) calculate that substantial asbestos exposure confers a relative risk of about 1.6 for colorectal cancer, consistent with the value seen in the largest ongoing cohort study of asbestos workers.” (Emphasis original.) See: Rosenstock, L. and Cullen, M.R. “Textbook of Clinical Occupational and Environmental Medicine,” p. 579 (W.B. Sanders Company) (1994). Cohort reference is to the insulation studies of Dr. Irving Selikoff, et al. that reported in 1964 in the Journal of the American Medical Association a threefold excess mortality from colorectal cancer among asbestos insulators. See Selikoff, I.J., Churg, J., Hammond, E.C., “Asbestos Exposure and Neoplasia,” JAMA 1964, 188:22-6

Knowing that an accurate factual record is as important to you as it is to us, we all request that you insert the references contained herein into the Senate Record and correct your misstatement.

Please feel free to contact me should you have any questions, or have any of your operatives call me. I would very much appreciate speaking to the source of your misinformation. Thank you for your anticipated thoughtful consideration of our request and correction of the Record.

With kind regards,

A handwritten signature in black ink, appearing to read "Gilbert L. Purcell", with a large, stylized flourish at the end.

Gilbert L. Purcell

GLP:jpn  
Enclosures

cc: Susie Purcell  
P.O. Box 2020  
Blanchard, OK 73010

# Federal Register

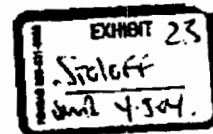
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July 12, 1989

Part III

## Environmental Protection Agency

40 CFR Part 763

Asbestos: Manufacture, Importation,  
Processing, and Distribution in  
Commerce Prohibitions; Final Rule



## ENVIRONMENTAL PROTECTION AGENCY

## 40 CFR Part 763

(OFTS-620360; FR-3476-3)

## Asbestos; Manufacture, Importation, Processing, and Distribution in Commerce Prohibitions

AGENCY: Environmental Protection Agency.

ACTION: Final rule.

**SUMMARY:** EPA is issuing this final rule under section 6 of the Toxic Substances Control Act (TSCA) to prohibit, at staged intervals, the future manufacture, importation, processing, and distribution in commerce of asbestos in almost all products, as identified in the rule. EPA is issuing this rule to reduce the unreasonable risks presented to human health by exposure to asbestos during activities involving these products. The rule requires that asbestos-containing products that are subject to the bans be labeled to promote compliance with and enforcement of the rule. The rule provides that exemptions from the rule's bans on manufacture, importation, processing, and distribution in commerce may be granted by EPA in very limited circumstances.

**DATE:** In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern time on July 28, 1969. The effective date of this rule is August 23, 1969, except for the information collection requirements of 40 CFR 763.173, 763.174, and 763.179. These information collection requirements have not been approved by the Office of Management and Budget (OMB) and are not effective until OMB has approved them. EPA will issue a notice in the future establishing an effective date for the information collection requirements.

**FOR FURTHER INFORMATION CONTACT:** Michael M. Stahl, Director, TSCA Assistance Office (TS-729), Office of Toxic Substances, Environmental Protection Agency, Rm. EB-44, 401 M Street SW., Washington, DC 20460. Telephone: (202-554-1404). TDD: (202-554-0631).

**SUPPLEMENTARY INFORMATION:** The preamble accompanying this final rule is divided into the following units:

- I. Authority
- II. TSCA Actions to Date
- III. Provisions of the Rule
  - A. General Provisions
  - B. Manufacture, Importation, and Processing Bans
  - C. Bans on Distribution in Commerce
  - D. Labeling

- E. Exemption Application Procedures
- F. Military Exemptions
- G. Recordkeeping
- IV. Summary of Analysis Supporting this Final Rule
- V. Regulatory Assessment
  - A. Health Effects and Magnitude of Exposure to Asbestos
  - B. Environmental Effects
  - C. Asbestos Substitutes
  - D. Economic Effects of the Rule
  - E. Other Options Considered
  - F. Summary of Individual Product Categories
- VI. Other EPA Statutes
- VII. Analysis under Section 8(a) of TSCA
  - A. Other Authorities Affecting Asbestos
  - B. EPA's Determination Under Section 8(a) of TSCA
- VIII. Enforcement
- IX. Confidentiality
- X. Rulemaking Record
- XI. References
- XII. Regulatory Assessment Requirements
  - A. Executive Order 12231
  - B. Regulatory Flexibility Act
  - C. Paperwork Reduction Act

This rule prohibits the manufacture, import, processing, and distribution in commerce of certain asbestos-containing products. The rule also requires that asbestos-containing products that are subject to this rule be labeled to facilitate compliance with and enforcement of the rule.

Public reporting burden for this collection of information is estimated to average less than 2 hours annually per firm over the 3-year period reviewed for the analysis of regulatory burden. This burden estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. This estimate of annual burden is a relatively low figure because of the small number of firms affected by the regulatory actions taken during the period reviewed for the analysis of regulatory burden. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Branch, PM-223, U.S. Environmental Protection Agency, 401 M Street SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503. Attention: Desk Officer for EPA.

- I. Authority
 

Section 8(a) of TSCA authorizes EPA to impose certain regulatory requirements on activities involving a chemical substance or mixture if EPA finds that there is a reasonable basis to conclude that the manufacture,

processing, distribution in commerce, use, or disposal of the chemical substance, or any combination of such activities, presents or will present an unreasonable risk of injury to human health or the environment. Section 8(a)(1) authorizes EPA to prohibit or limit the manufacture, processing, or distribution in commerce of substances or mixtures if EPA finds that these activities pose an unreasonable risk. Section 8(a)(2) authorizes EPA to prohibit or limit such activities for a particular use of such substances or mixtures. Section 8(a)(3) authorizes EPA to require labels for such substances or mixtures. Sections 8 and 8(a) authorize EPA to require the maintenance of records related to enforcement of EPA actions under section 6. These sections of TSCA provide EPA the authority to issue this rule.

## II. TSCA Actions to Date

EPA issued an Advance Notice of Proposed Rulemaking in the Federal Register of October 17, 1979 (44 FR 67061), announcing its intent to explore the use of section 6 of TSCA to reduce the risk to human health posed by exposure to asbestos. EPA then issued a reporting rule under section 8(e) of TSCA in the Federal Register of July 30, 1982 (47 FR 33207, 40 CFR 763.60), to collect information on industrial and commercial uses of asbestos. Information collected under that rule, as well as analyses developed by EPA and other organizations, were evaluated and used to support a proposed rule, published in the Federal Register of January 23, 1988 (51 FR 3736).

In the proposed rule EPA found that exposure to asbestos poses an unreasonable risk to human health and discussed regulatory options for prohibiting or restricting the mining and importation of bulk asbestos and the manufacturing, importation, and processing of asbestos-containing products as means of reducing the risk. The following options were discussed in the proposed rule:

1. Two options involving bans of some products soon after promulgation of the final rule and a phase out of others over 10 years by means of a permit system for asbestos use.
2. A 2-stage ban, with the first ban on asbestos construction products and clothing, to begin soon after promulgation of the final rule and the second ban on friction products, to begin in 5 years, and after promulgation of the final rule, the collection of additional data on other products.
3. A 3-stage ban on all asbestos products to begin soon after the

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diseases are not as great as for lung cancer and mesothelioma. All of these asbestos-related diseases are life-threatening or disabling and cause substantial pain and suffering.

The conclusions reached by EPA regarding the health effects of asbestos exposure represent a widely accepted consensus of opinions of health agencies, scientific organizations, and independent experts. The major health effects of asbestos are summarized below.

**a. Lung cancer and mesothelioma.** Lung cancer has been responsible for the largest number of deaths attributable to occupational exposure to all of the principal commercial asbestos mineral types: chrysotile, amosite, crocidolite, and anthophyllite. Excess lung cancers have been documented among workers involved in asbestos mining and milling and in the manufacturing and use of a variety of asbestos products. Lung cancer risk appears to increase with both the level and duration of exposure. The latency period for the disease is generally 20 years or more after exposure. This means that lung cancer usually does not manifest itself until 20 years after the disease-initiating exposure. Most persons who develop lung cancer die within 2 years of diagnosis.

While both asbestos and cigarette smoking can separately increase risk of lung cancer, together they appear to interact synergistically to multiply lung cancer risk in humans. Commenters have suggested that smoking should be controlled to reduce the very high lung cancer risk due to combined asbestos exposure and smoking. However, even complete control of the smoking factor, if possible, would leave a substantial health risk since the asbestos-related risk of lung cancer to nonsmokers and of mesothelioma (which is apparently not affected by smoking) would remain.

Mesothelioma is a rare cancer of the lining of the lung (pleural mesothelioma) or abdominal cavity (peritoneal mesothelioma). Mesothelioma has been associated with occupational exposure to chrysotile, amosite, and crocidolite. Epidemiological studies suggest that mesothelial risk rises rapidly with time from the onset of exposure. Risk also increases with both intensity and duration of exposure. The latency period for the disease is generally between 25 and 30 years. In almost all instances, the disease is rapidly fatal, with survival times of less than 2 years after diagnosis. There is no evidence that cigarette smoking increases the risk of developing asbestos-induced mesothelioma.

Most epidemiological studies have been conducted on occupational populations exposed to high airborne concentrations of asbestos for relatively long periods of time. However, short-term occupational exposures have been shown to cause serious health effects. For example, one group of asbestos factory workers with less than 2 months of occupational exposure had a two-fold increase in lung cancer risk (Ref. 4). Also, many documented cases of mesothelioma have been linked to extremely brief exposures to relatively high concentrations of asbestos (Ref. 1).

There is also direct evidence of adverse health effects from non-occupational asbestos exposure. Increased risk of pleural abnormalities and mesothelioma have been observed in families of asbestos workers, presumably due to the dissemination of fibers in the home from contaminated work clothes. Mesothelioma have also been documented in populations whose only identified exposure was living near asbestos mines or asbestos product factories, or shipyards with heavy asbestos use (Ref. 1).

Animal studies confirm the epidemiological findings regarding the health effects of asbestos exposure. All commercial forms of asbestos have been shown to produce lung tumors and mesothelioma in laboratory animals with no substantial differences between the form of asbestos forms in carcinogenic potency.

**b. Gastrointestinal cancer.** A number of epidemiological studies have documented significant increases in the incidence of gastrointestinal cancer due to occupational exposure to asbestos. Gastrointestinal cancers consist largely of cancers of the esophagus, stomach, colon, and rectum. However, the magnitude of gastrointestinal cancer risk is lower than that of lung cancer or mesothelioma and no dose-response data are available.

A number of commenters argued that the evidence indicating a positive association between gastrointestinal cancer and asbestos exposure is weak and inconclusive. They indicated that unidentified facts may cause the excess gastrointestinal cancers. Commenters suggested that many of the excess cancers attributed to gastrointestinal sites may be due to misdiagnosis of peritoneal mesothelioma. Other commenters contended that in the absence of any positive experimental evidence, the epidemiology data alone do not support the conclusion that exposure to asbestos can cause gastrointestinal cancer.

EPA recognizes that the evidence supporting an association between gastrointestinal cancer and asbestos exposure is not as strong as that which is available to support an association between asbestos exposure and lung cancer and mesothelioma. However, after weighing available information, EPA believes that there is evidence of a strong causal relationship between asbestos exposure and gastrointestinal cancer excess. This evidence includes the following: (1) A statistically significant increase in gastrointestinal cancer was found in 10 of 23 epidemiological studies. (2) A consistent relationship exists between increased gastrointestinal cancer risk and increased lung cancer risk (approximately 10 to 30 percent of the lung cancer excess). (3) It is biologically plausible that asbestos could be associated with these tumor sites, because it is conceivable that the majority of fibers inhaled are cleared from the respiratory tract and subsequently swallowed, allowing the fibers to enter the gastrointestinal tract (Ref. 5). Additionally fibers may be swallowed directly. (4) One study demonstrated some evidence of carcinogenicity in male rats fed diets containing intermediate range size chrysotile asbestos (63 percent 10 microns in length) (Ref. 6).

Further, EPA does not accept the argument that all gastrointestinal cancers identified in the epidemiology studies described above are the result of misdiagnosis. Cancers of some gastrointestinal cancer sites (e.g., stomach and pancreas) could be the result of misdiagnosis of peritoneal mesothelioma. However, this does not account for all of the excess cancers seen at sites such as the colon or rectum. OSHA, in its final rule lowering the asbestos PEL concluded that the studies conducted to date "constitute substantial evidence of an association between asbestos exposure and a risk of incurring gastrointestinal cancer." EPA agrees with this conclusion.

**c. Cancers at other sites.** Increased risk of cancers other than mesothelioma and lung and gastrointestinal cancers have been observed in populations occupationally exposed to asbestos. An excess of laryngeal cancer in asbestos workers has been reported in a number of studies (Ref. 2). Available data, however, indicate that there may be an interaction between smoking and asbestos exposure in the etiology of laryngeal cancer. Elevated risk of kidney cancer has also been observed in two epidemiological studies (Refs. 7 and 8). In addition, an increased incidence of



American Journal of Epidemiology  
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Vol. 162, No. 9  
DOI: 10.1093/aje/kw285  
Advance Access publication September 21, 2005

## Original Contribution

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

Oluremi A. Aliyu<sup>1</sup>, Mark R. Cullen<sup>1</sup>, Matt J. Barnett<sup>2,3</sup>, John R. Balmes<sup>4,5</sup>, Brenda Cartmel<sup>1</sup>, Carrie A. Redlich<sup>1</sup>, Carl A. Brodtkin<sup>3</sup>, Scott Barnhart<sup>3,6</sup>, Linda Rosenstock<sup>7</sup>, Leslie Israel<sup>8</sup>, Gary E. Goodman<sup>2,3,9</sup>, Mark D. Thornquist<sup>2,3</sup>, and Gilbert S. Omenn<sup>10,11</sup>

<sup>1</sup> Yale Occupational and Environmental Medicine Program and the Cancer Center, Yale University School of Medicine, New Haven, CT.

<sup>2</sup> Fred Hutchinson Cancer Research Center, Seattle, WA.

<sup>3</sup> Occupational and Environmental Medicine Program, University of Washington, Seattle, WA.

<sup>4</sup> Department of Medicine, School of Medicine, University of California, San Francisco, San Francisco, CA.

<sup>5</sup> Center for Occupational and Environmental Health, University of California, Berkeley, Berkeley, CA.

<sup>6</sup> Harborview Medical Center, Seattle, WA.

<sup>7</sup> School of Public Health, University of California, Los Angeles, Los Angeles, CA.

<sup>8</sup> Center for Occupational and Environmental Health, University of California, Irvine, Irvine, CA.

<sup>9</sup> Swedish Medical Center Cancer Institute, Seattle, WA.

<sup>10</sup> Departments of Internal Medicine and Human Genetics, School of Medicine, University of Michigan, Ann Arbor, MI.

<sup>11</sup> Department of Public Health, School of Public Health, University of Michigan, Ann Arbor, MI.

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 ( $p \leq 0.03$  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

Correspondence to Dr. Mark R. Cullen, 135 College Street, New Haven, CT 06510 (e-mail: mark.cullen@yale.edu).

(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 1/4.54); 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, shipfitting, 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, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, 3/p, 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.

870 Aliyu et al.

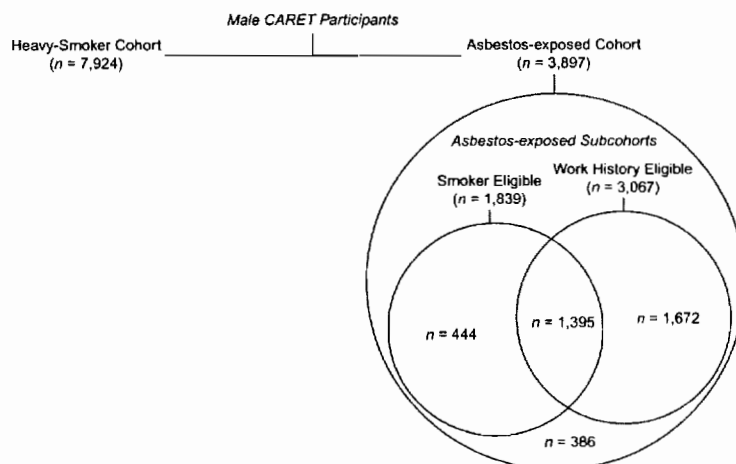


FIGURE 1. Major cohorts of male participants enrolled in the Beta-Carotene and Retinol Efficacy Trial (CARET) (Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004) and subcohorts within the asbestos-exposed cohort. 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  $\beta$  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. These 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

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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 <sup>2</sup> )	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.

y 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.

z 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) <sup>§</sup>	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 <sup>2</sup> )	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.

y 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.

z 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

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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.)	RRy	95% CIy,z	p value
<b>At-risk population</b>					
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	
<b>Pleural abnormality {</b>					
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	
<b>Radiographic profusion rating category (major categories)#</b>					
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/p	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.

y RR, relative risk; CI, confidence interval.

z 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.

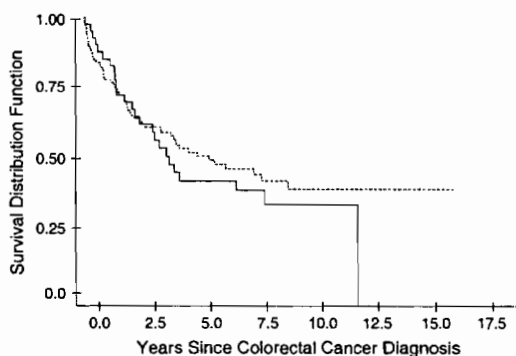


FIGURE 2. Postdiagnosis colorectal cancer survival in two subpopulations of the Beta-Carotene and Retinol Efficacy Trial (Seattle, Washington; Irvine, California; New Haven, Connecticut; San Francisco, California; Baltimore, Maryland; and Portland, Oregon, 1985–2004). Cases in the asbestos-exposed smoker-eligible 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.)	RRy,z	95% CIy	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/p	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.

y RR, relative risk; CI, confidence interval.

z 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 especially 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

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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.)	RRy	z	95% CIy	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.

y RR, relative risk; CI, confidence interval.  
 z 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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IRWIN L. STOLOFF, M.D., F.A.C.P.  
628 CHELTEN HILLS ROAD  
ELKINS PARK, PA 19027

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215-6351634  
Fax: 215-635-2174

October 25, 2004

Brayton & Purcell  
222 Rush Landing Road  
Novato, CA 94948

Attn: Ms. Rogers

Re: Ralph Pierce  
Date of Birth: 7/28/34

Dear Ms. Rogers:

I received five booklets of medical records concerning Ralph Pierce and I am asked to determine if he had an asbestos disease.

Mr. Pierce was exposed to asbestos between 1953-1997 while working as a machinist and toolmaker at various job sites including shipyards and later, water treatment plant. During this period of time he worked around insulation, packing, gaskets, blankets and brakes creating dust to which he was exposed.

He is an ex-cigarette smoker who stopped smoking in 1972.

There is a family history of breast cancer in his mother and sister and prostate cancer in two brothers.

Dr. Breyer, a B reader radiologist reviewed films of 11/23/01 and found interstitial fibrosis and bilateral pleural thickening.

Dr. Jay, an occupational medicine specialist examined Mr. Pierce on 2/9/03. He noted the asbestos exposure and brief smoking history of less than one pack per day for two years. There was cough and shortness of breath and a history of colon cancer resected December 2002. He quotes Dr. Powers' chest x-ray report of pleural thickening. Spirometry was normal. Dr. Jay's opinion was that Mr. Pierce had asbestos pleural disease.

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Dr. Meyers examined Mr. Pierce on 6/30/03. He reported cough and shortness of breath, noted the asbestos history, and found a scar in the abdomen from previous colon surgery. He reviewed all chest x-rays and found that they were normal. Pulmonary function studies were normal. He did not find evidence of asbestos disease and does not believe it is generally accepted that asbestos is a causative factor in colon cancer.

Dr. Moscow, a radiologist reviewed chest x-rays of 8/16/04 which he found to be normal.

San Pablo Medical Center records were reviewed. There was a hospital admission 12/11/02 for cramps and bloody diarrhea. A colonoscopy showed a mass in the splenic flexure of the colon, which was resected by partial left colectomy. The pathologist confirmed an invasive adenocarcinoma with 2 of 43 lymph nodes positive for tumor, a T2N1 colorectal cancer.

Mr. Pierce was treated postoperatively between January 2003 and August 2003 with adjuvant chemotherapy.

Pulmonary function studies of 3/20/03 in contrast to Dr. Meyer's studies showed a small reduction in carbon monoxide diffusion at 71% of normal.

Dr. Nachtwey did an asbestos evaluation 12/9/02 and reported cough and shortness of breath with negative chest x-rays.

Dr. O'Connor's records were reviewed. On 5/24/04 there was right upper quadrant abdominal pain, a rising CEA and CT evidence of liver metastases. Colonoscopy showed a benign polyp in the colon, which on biopsy proved to be a tubulovillous adenoma.

Mr. Pierce also experienced a deep venous thrombosis of the subclavian and jugular vein related to a venous catheter, which prompted the use of coumadin.

Work history, Interrogatories and depositions of Mr. Pierce were reviewed. They indicate that Mr. Pierce has tightness in the chest and chest congestion.

Past medical history includes diabetes mellitus, hypertension, hypothyroidism, GERD, deep venous thrombosis and foot surgery.

In summary, Mr. Pierce, who is currently 70 years of age was exposed to asbestos beginning in 1953. There is no family history of colorectal cancer. He

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was found to have colorectal cancer in 2002 approximately 50 years after first asbestos exposure. Although there is some controversy about the status of his chest x-rays at least two radiologists found bilateral pleural thickening and reported cough and shortness of breath.

The question arising in Mr. Pierce's case is the cause of his colorectal cancer, which has spread to his liver and is currently a Dukes D cancer.

Asbestos fiber exposure is a known risk factor for colorectal cancer.

Beginning with Selikoff's report on an increase mortality from colorectal cancer in insulation workers with a standard mortality ratio of 1/55, there have been other confirmatory reports showing an increase mortality from this type of cancer in workers exposed to asbestos. Puntoni in Genoa, Italy shipyard workers also demonstrated an increase death rate from colon cancer. When using the local hospital staff as controls the mortality ratio was 4.8 times the expected. McDonald, in Quebec asbestos miners, demonstrated a mortality ratio for colorectal cancer in those with the greatest asbestos exposure who had a mortality ratio of 5.26 times the expected. McDonald also demonstrated a dose response relationship since those with lesser asbestos exposure did not demonstrate an increased death rate from colorectal cancer. Finkelstein, studying the mortality among employees of an Ontario asbestos cement factory, reported a mortality ratio of 3.2 and 3.7 in older workers exposed beyond 15 years from first exposure for all gastrointestinal cancers in contrast to a group with no asbestos exposure.

Ehrlich reported the findings of asbestos bodies in the colon cancers of asbestos workers not found in colon cancers of non-asbestos workers demonstrating that asbestos bodies can penetrate the colon and land in areas where colon cancer develops. The entire problem of asbestos in gastrointestinal malignancy has been reviewed by the Environmental Protection Agency's scientists and reported in the Federal Registry of July 1989. It is their conclusion that there is sufficient evidence that asbestos is a cause of all gastrointestinal malignancy including colorectal cancer.

With these facts in mind it is my opinion within a reasonable degree of medical certainty that in the absence of a hereditary history of colorectal cancer or chronic inflammatory bowel disease, asbestos is a causative factor in Mr. Pierce's colorectal cancer.

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It is also my opinion within a reasonable degree of medical certainty that Mr. Pierce had asbestos pleural disease, cough and shortness of breath with a carbon monoxide diffusion defect caused by asbestos fiber inhalation.

Mr. Pierce's prognosis for surviving colorectal cancer is poor since he already has liver metastases. He also remains at risk for other asbestos related cancers and for progressive fibrosis of the lungs and pleura caused by his asbestos fiber exposure.

Each and every exposure to asbestos constitutes a significant contributing factor to the asbestos related disease that has been diagnosed.

Thank you for the opportunity to review Mr. Pierce's medical records.

Sincerely yours,



Irwin L. Stoloff, M.D., F.C.C.P.

ILS:cgf

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