The Carotene and Retinol Efficacy Trial (CARET) to Prevent Lung Cancer in High-Risk Populations: Pilot Study with Asbestos-exposed Workers

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Abstract
Pilot studies are an essential component for major chemoprevention trials. Prior to initiating the multicenter Carotene and Retinol Efficacy Trial to assess the effectiveness of β-carotene and retinol for preventing lung cancer, we conducted pilot studies in Seattle between 1985 and 1988 in two high-risk populations: current and former heavy smokers and asbestos-exposed workers. The Asbestos Workers Pilot Study for the Carotene and Retinol Efficacy Trial demonstrated that recruitment of asbestos-exposed participants with relevant risk factors was feasible from identified sources. We documented negligible toxicity and high adherence with the protocol, schedule, and intervention. Results from the pilot led to extension of the placebo run-in period, changes in the eligibility criteria, improvements in recruitment strategies and scheduling, elimination of stratification by risk factors in randomization, modifications of study vitamin dosage and of side effects monitoring, and refinement of trial design parameters for Carotene and Retinol Efficacy Trial. The Smokers Pilot is reported in the accompanying article (G. E. Goodman et al., Cancer Epidemiol. Biomarkers & Prev., 2: 389-396, 1993).

Introduction
Chemoprevention trials require a large number of participants, long intervention and follow-up periods, and a capable infrastructure. Carefully designed pilot studies are essential to evaluate recruitment from various identified sources, adherence of randomized participants with the regimen, potential toxicity from the agents, and many other facets of the protocol. Two placebo-controlled, double-blind, randomized pilot studies were performed in Seattle between June 1985 and June 1988 to assess the feasibility of CARET in populations at high risk for lung cancer: current and former heavy smokers and asbestos-exposed workers.

Lung cancers accounted for more than 130,000 deaths in 1991 in the United States. 27% of all cancer deaths and 6% of total deaths (1). Occupational exposures to asbestos are estimated to cause 4000 to 6000 excess lung cancer deaths/year (2, 3). Five-year survival with lung cancer remains less than 15% (4); thus, the National Cancer Institute Year 2000 Strategic Plan accorded prevention the highest priority for lung cancer (4). Prevention strategies include discouraging initiation of smoking, promoting smoking cessation, minimizing occupational exposures to asbestos and certain other agents, and chemoprevention in those millions of persons already highly exposed to smoking and/or asbestos. A large literature supports the decision to test β-carotene and vitamin A as chemopreventive agents in these populations (5-9).

The Asbestos Workers Pilot Study of men with occupational exposures to asbestos was designed to identify adequate sources of interested eligible men, gain data on the exposure history and risk factors for lung cancer in the available populations, demonstrate recruitment from occupationally defined sources, evaluate adherence, and monitor symptoms and signs and laboratory parameters to evaluate safety. The phase II Smokers Pilot Study emphasized toxicity assessment, as described in the accompanying article (Goodman et al.). The results from both pilots were essential to the decision in 1988 to expand recruitment into the long-term efficacy study, CARET, a phase IV chemoprevention trial conducted in six study centers (Baltimore, MD: Irvine, CA: New Haven, CT; Portland, OR; San Francisco, CA; and Seattle, WA) (see Refs. 10, 11). We present here data to the end of the pilot period in June 1988.

Materials and Methods

Eligibility. Eligibility criteria were being male, aged 45 to 74 years; having a history of asbestos exposure beginning at least 15 years prior to entry; and having either a chest x-ray positive for changes consistent with asbestos-related fibrosis of the parenchyma or the pleura or a history of at least 5 years in a high-risk trade. Chest x-ray abnor-
malignancies were classified using ILO criteria: at least bilateral 3-mm pleural thickening or unilateral 5-mm pleural thickening and/or profusion ≥1,0] (12). We identified the following eight high-risk trades in the Puget Sound area: asbestos workers; shipyard boilermakers; shipyard electricians; shipscalers; shipfitters; plumbers/pipefitters; platerboard workers; and sheetmetal workers. Since essentially all persons meeting the age and exposure criteria were male, the study was limited to men. There was no possibility that these agents might increase cancer risk at some sites, and assure participants that they were able to terminate their participation at any time. Posterior–anterior and lateral chest X-rays were obtained at a nearby facility to evaluate eligibility and risk factors. The X-rays were read by a radiologist to rule out prevalent lung cancers and then by consensus of two readers (L. R. and S. B.) trained in the ILO system (12). Spirometry

<table>
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<tr>
<th>Source</th>
<th>No. Mailed</th>
<th>Responses</th>
<th>Eligible for phone contact</th>
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<tr>
<td></td>
<td></td>
<td>n</td>
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<td>n</td>
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<tr>
<td>No. 7 asbestos workers</td>
<td>328</td>
<td>130</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
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<td>2823</td>
<td>743</td>
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<td>273</td>
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<td>698</td>
<td>178</td>
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<td>92</td>
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<tr>
<td>Self-referrals</td>
<td>111</td>
<td>106</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>Radio/newspaper</td>
<td>53</td>
<td>50</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>11,750</td>
<td>2990</td>
<td>25</td>
<td>1580</td>
</tr>
</tbody>
</table>

* Selected to be age specific.

† Access to specific information about asbestos-related disease. Percentages based on denominator of all persons sent mailings by each source.

‡ Sent 1 mailing only; for attorneys, 1 of 3 groups sent only 1 mailing.

** Table 1 Recruitment, by source

Enrollment (First Visit). The first visit involved an explanation of the study, review and acceptance of the informed consent document, collection of occupational health history and other baseline data, physical examination, and blood collection for liver function tests and carotene and retinoid determinations. The informed consent document outlined the aims of the study, explained the known high-dose toxicity risks, mentioned the possibility that these agents might increase cancer risk at some sites, and assure participants that they were able to terminate their participation at any time. Posterior–anterior and lateral chest X-rays were obtained at a nearby facility to evaluate eligibility and risk factors. The X-rays were read by a radiologist to rule out prevalent lung cancers and then by consensus of two readers (L. R. and S. B.) trained in the ILO system (12). Spirometry
was performed according to recommended standards (13) at both the first visit and the second (randomization) visit. As a recruitment feature, visit findings were summarized for the individual and shared with his physician.

**Intervention Protocol.** The Asbestos Workers Pilot Study was a two-arm randomized comparison of the combination of 15 mg \( \beta \)-carotene and 25,000 international units of retinol against placebos taken daily. Retinol and \( \beta \)-carotene or their identical appearing placebos were distributed as separate capsules in blister cards. Hoffman-LaRoche, Nutley, NJ, provided both the active and placebo study vitamins and performed quality control analyses.

As in the Physicians Health Study (Hennekens in Ref. 14), we used a 2-month enrollment run-in period on placebo to evaluate adherence to the intervention and to the initial schedule. Randomization occurred at the second visit. Thereafter, participants were contacted every 2 months, alternating telephone interviews and study center visits. Using a standard questionnaire, follow-up information on dosage taken and on symptoms and signs potentially due to toxicity was collected according to protocol instructions.

**Monitoring of Adherence to the Intervention.** Staff counted capsules remaining in the 31-day blistercards returned by participants; if the blistercards were not brought to the visit, the participant’s self-report of days missed was recorded. Annual blood draws permitted analyses by the assay we developed to measure \( \alpha \) and \( \beta \)-carotene, retinol, and retinyl palmitate in a single column, isocratic high-performance liquid chromatography method (15).

**Monitoring of Potential Toxicity.** We developed a symptom assessment questionnaire for skin redness, skin dryness or itching, skin yellowing, lip chapping, headaches, anxiety, depression, fatigue, bone pain, vomiting, change in bowel movements, nosebleeds, hair loss, appetite, and weight change; a companion scheme was designed for physical findings of redness, dryness, or yellowing of the skin, dryness of the lips, and bone tenderness (16). Information on these 15 symptoms was collected at first visit and every 2 months thereafter. SGOT, alkaline phosphatase, and nonfasting serum cholesterol and triglycerides were determined at the first visit, 4 and 12 months after study end, and every 2 months thereafter. Monitoring of Potential Toxicity. We developed a symptom assessment questionnaire for skin redness, skin dryness or itching, skin yellowing, lip chapping, headaches, anxiety, depression, fatigue, bone pain, vomiting, change in bowel movements, nosebleeds, hair loss, appetite, and weight change; a companion scheme was designed for physical findings of redness, dryness, or yellowing of the skin, dryness of the lips, and bone tenderness (16). Information on these 15 symptoms was collected at first visit and every 2 months thereafter. SGOT, alkaline phosphatase, and nonfasting serum cholesterol and triglycerides were determined at the first visit, 4 and 12 months after randomization, and annually thereafter. This monitoring scheme was based on known high-dose gastrointestinal, hepatic, nervous system, and skin toxicities of retinoids (17, 18) and is discussed in detail in the accompanying paper on the CARET Smokers Pilot Study (Goodman et al.).

**Statistical Aspects.** Randomization was stratified by smoking history (never smoked), years since first exposure to asbestos (15–30 and >30 years), parenchymal fibrosis (chest x-ray ILO grade profusion \( \geq 1,0 \), \( \geq 1,0 \)), and recruitment source (medical, workers’ compensation agencies, Navy, unions, and other). Differences between the intervention arms were assessed using \( \chi^2 \) or Fisher’s exact tests (2-tail) for categorical variables, Student’s t-test for continuous variables, and Kaplan-Meier plots for comparisons over time.

**Results**

**Recruitment and Randomization.** From June 1985 to August 1988, 816 eligible participants were randomized into the Asbestos Workers Pilot Study. Table 1 shows the response rates to recruitment mailings and numbers of participants randomized by recruitment source. Of the 1580 respondents potentially eligible, 1009 came for the first visit, 832 returned for the second visit, and 816 were randomized.

More than 20% of the mailings from physicians and clinics led to randomizations, compared with about 15% from workers’ compensation programs and plaintiffs attorneys. 7% from the Navy program, and 1–7% from the various union rolls. The largest numbers of participants came from the union sources, since those mailings were much larger. The mailing from the United States Navy Asbestos Surveillance Program was approved by the Navy Environmental Health Command and was the first use of data from that database.

Since the rate of cross-mailings from multiple sources is unknown and timing of mailing(s) to multiple sources was variable, comparison of yields from various sources must be made with caution. Sources from which age-specific mailings could be made (physicians, clinics, and compensation groups) had higher rates of response, eligibility, and randomization than did the unions; unlike the unions, these sources also had access to specific information about asbestos-related disease, which was...
used in preparing the mailing lists. Finally, not all sources made second mailings (Table 1).

Table 2 shows the distributions of baseline characteristics for randomized participants by intervention arm (blind maintained). The arms are well balanced, with no statistically significant differences. The mean age at the time of randomization was 58; of 816 randomized participants, 93% were white and 3% were black. The distribution of smoking status among our participants was 16% never-smokers, 62% former smokers, and only 22% current smokers. Former smokers were much more prevalent than expected, with a mean of 19 years since permanent cessation (11% quit fewer than 5 years before randomization, 13% had quit for 5 to 9 years, 16% had quit for 10 to 14 years, and 60% had quit for 15 or more years). For the cohort of 680 who had ever smoked, the mean of pack-years was 33 and the mean number of cigarettes/day was 23; for the entire group of 816 men, the means were 28 years and 19 cigarettes/day, respectively.

Most participants (57%) were eligible by both the x-ray and occupational history criteria; 95% had worked at least 5 years in 1 or more of our 8 designated high-risk trades. The mean years since first asbestos exposure for all participants was 35, with an average of 25 years spent in a high-risk trade. Chest x-rays that were positive for radiographic involvement and spirometric evidence of functional impairment, and of both with years since first occupational exposure to asbestos. These data on risk factors demonstrate that a highly exposed population was recruited.

Of the 193 individuals who had a first visit but were not randomized (incomplete enrollments), 2 died, 95 were not interested, and 96 were ineligible (57 due to inadequate exposure; 25 due to abnormal liver function tests; and 8 of the rest due to recent cancer or liver disease). From the information recorded at first visits, persons with incomplete enrollment were indistinguishable from those randomized with regard to mean age, percent non-white, mean pack-years, cigarettes/day, and (among former smokers) mean years quit; they had a much higher percentage of negative chest x-rays or inadequate trades history for asbestos exposure.

Adherence. Staff count of capsules remaining in 31-day blister cards or self-report of days missed was the basis of the capsule consumption measurement of adherence. The capsule consumption rate at time t is defined to be the fraction of full dose of the study vitamins taken by participants whose follow-up is at least t. Overall rates were 98% at randomization, 86% at 12 months, and 82% at 24 months, with no statistically significant differences between arms.

In Table 3, the differentiation between arms indicates that serum levels of β-carotene and retinyl palmitate responded promptly to the intervention. In the active arm, β-carotene mean concentrations increased from about 200 ng/ml at first visit to 1500 ng/ml at the 4-month visit and then continued gradually upward to nearly 1700 ng/ml at the second annual visit. Because of marked skewness of the distributions, we present median and 10th and 90th percentile values in Table 3 rather than means with SD or confidence intervals. The 90th percentile of serum β-carotene in the placebo arm corresponded to the 10th percentile in the active arm, at about 400 ng/ml. Mean retinyl palmitate levels rose from approximately 70 to 280 ng/ml in 4 months and stabilized at about 260 ng/ml. α-carotene levels more than doubled. For all three analytes, serum levels in the placebo arm remained close to their baseline values resulting in statistically significant differences (P < 0.01) between arms at each postrandomization visit. The modest, statistically significant increase in median serum β-carotene levels in the placebo arm (Table 3) from 144 ng/ml at first visit to 187 ng/ml at 24 months is not explained by the dietary intake of β-carotene as measured by our food

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Concentrations of carotenes and retinoids (ng/ml) by months since randomization*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since randomization</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>First visit</td>
<td>810</td>
</tr>
<tr>
<td>4</td>
<td>721</td>
</tr>
<tr>
<td>12</td>
<td>624</td>
</tr>
<tr>
<td>24</td>
<td>328</td>
</tr>
</tbody>
</table>

* Concentrations are medians with 10th and 90th percentile values in parentheses.
Excluding deaths.

As expected, which accounts for much of the variability in the data, data not shown) and does not persist with additional follow-up beyond the pilot period. The analyses were performed on nonfasting samples obtained at variable intervals from the time the daily capsules were ingested, which accounts for much of the variability in the data, particularly for retinyl palmitate, which is formed by esterification of retinol in the intestine. As expected, mean retinol concentrations were maintained within a narrow range (720-800 ng/ml), although a modest increase from baseline and statistically significant differences between arms were observed. Previous studies have shown that, with high doses of oral retinol, serum retinol concentrations remain relatively stable, while concentrations of the retinyl esters (retinyl palmitate and retinyl stearate) increase progressively (17).

About 15% of the participants became inactive by discontinuing taking their study vitamins. The most frequently cited reasons, listed in Table 4, are symptoms considered by the participant to be possibly related to the study vitamins. For only ten was the dose terminated due to threshold symptoms according to the symptom management protocol. Analyses of the time course to going off vitamins and the mean and maximum symptom grades immediately prior to becoming inactive gave no statistical evidence of differences between arms for any of these parameters.

### Toxicity Monitoring

The monitoring for potential toxicity is described in detail in the accompanying article (Goodman et al.). For analyses, relevant symptoms and signs were grouped into eight categories: skin redness, itching, and dryness/nosebleeds; skin yellowing; headaches; weight and appetite loss; psychological symptoms (anxiety, depression, fatigue); bone pain; nausea and vomiting; and change in bowel habits. Except for bowel movements, there was no statistically significant difference between the treatment arms in rates.

The threshold laboratory values which triggered symptom management were 100 and 195 international units/liter for SGOT and alkaline phosphatase, respectively. There was one active-arm participant with elevated SGOT, and there were two with elevated alkaline phosphatase (one in each arm). Mean values and SD over the whole pilot period were 25 (±10) international units/liter for SGOT and 84 (±22) international units/liter for alkaline phosphatase, with no differences between baseline and postrandomization values for SGOT and a slight increase in alkaline phosphatase from 82 (±21) at first visit to 94 (±26) international units/liter at 24 months in the active arm. Nonfasting cholesterol and triglyceride serum values were monitored but not used to reduce dosage. Mean values over all visits were 235 (±44) mg/deciliter for cholesterol and 227 (±189) mg/deciliter for triglycerides; 80 participants had total cholesterol exceeding 300 mg/deciliter, and 23 had triglycerides exceeding 800 mg/deciliter postrandomization, again with no statistically significant differences between arms. Given the accumulation of vitamin A in the liver, we continue in CARET to monitor carefully for potential toxicity associated with cumulative dose in those participants who continued to be active in CARET after the pilot phase. No such evidence has arisen through mid-1992; semiannual reports are scrutinized by the external CARET Safety and Endpoints Monitoring Committee.

### Discussion

The Asbestos Workers Pilot Study for CARET demonstrated that the combination of recruitment sources identified in Seattle could yield a substantial number of randomized participants. This recruitment strategy seemed highly feasible for additional geographic areas of the country with substantial shipyard workforces and other potential sources available to academically based occupational medicine clinics. When feasible, we used a pair of mailings from a single recruitment source, since there was a good increment from the second mailing (17.2% responded to first mailings and 13.0% responded to second mailings). Initially, we screened lists to protect previous nonrespondents from another round of invitations from a new recruitment source; however, these considerable staff costs were unwarranted, since subsequent invitations from sources, the lists of which could not be prechecked, often elicited a positive response. Out-of-date mailing lists were a tremendous problem, as were union lists that could not be sorted by age or asbestos exposure.

By comparison with the best-studied asbestos-exposed cohort, the 17,800 insulators followed for many years by Selikoff et al. (22) at Mount Sinai Medical Center in New York, the randomized participants in the CARET Asbestos Workers Pilot Study have similar proportions of...
positive chest x-rays, more years of exposure in high-risk trades (although not all thought to be as high risk as the insulators), and more years since first exposure. The pilot study participants had a mean age at randomization 10 years greater than the Selikoff cohort; such an age difference is associated in the general population with a 3-fold higher lung cancer risk (23).

The CARET Asbestos Worker Pilot participants had a lower current smoking prevalence than the Selikoff cohort of insulators. Our cohort had 84% ever-smokers, but only 22% current smokers, whereas among the 8220 insulators who answered a smoking history questionnaire 83% were ever-smokers and 54% were current smokers. Apparently, widespread advice to stop smoking was successful among our high-risk men, beginning 20 or more years ago, at least among those who volunteered for our study.

Adherence to the intervention was excellent. Capsule consumption rates were similar for the active and placebo arms, as was adherence to the CARET visit schedule. The serum concentrations of β-carotene and of retinyl palmitate were increased substantially by the dosage administered. Despite variation in dietary intake and modest supplemental non-CARET vitamin intake, the intervention dominates these other sources of variation.

Careful monitoring for toxicity showed no symptoms, signs, or liver dysfunction that could be attributed to the intervention, except for very mild skin yellowing. These findings were highly reassuring.

No comments are warranted about endpoints or potential efficacy from the pilot phase of CARET. Fastidious collection of endpoints data was begun in 1989.

The combined results of the Smokers Pilot Study and the Asbestos Workers Pilot Study became the basis for CARET, which aims to recruit a total of 4,000 asbestos-exposed workers and 13,700 smokers. The lessons from the pilot studies were essential in justifying the full-scale CARET and in making numerous changes for the benefit of the participants and for improvement of the cost effectiveness of the entire protocol.

We decided not to add to the complexity of the randomization process in CARET by continuing with stratification by risk factors. With recruitment goals at each of the three major asbestos study centers of 800 to 1000 participants, the likelihood of any serious noncompatibility of treatment arms was small. As CARET nears its recruitment goals (10), the intervention arms continue to be well balanced with respect to all baseline characteristics at each study center.

In the transition to CARET, we reduced the maximal age from 74 to 69 years in order to ensure longer average follow-up and in recognition that part of the excess lung cancer risk of asbestos exposure is a shift to younger ages of the lung cancer incidence curve (3). The low smoking prevalence in the pilot led us to require that all asbestos-exposed men newly recruited to CARET must be smokers or ex-smokers who quit within the previous 15 years (9–11). Fifteen years was chosen, since the reemergence of asbestos fibers is hypothesized to extend the duration of high-hazard smoking exposure (9, 10, 16).

In CARET, we increased the β-carotene dose for asbestos-exposed workers to 30 mg/day, the same as in the Smokers Pilot. The amount of vitamin A administered remained at the pilot dosage of 25,000 international units/day. Negative comments about taking two capsules led us to work with the pharmaceutical company and packagers to combine β-carotene with retinyl palmitate (rather than retinol) in a single compatible capsule for CARET. We also increased the run-in period to 3 months and made the contacts every 3 months in the first year and every 4 months thereafter, rather than every 2 months, based on the high adherence and negligible toxicity in the pilot study.

The CARET informed consent document and the protocol continue to be based upon careful monitoring for potential toxicity associated with cumulative dose. This approach is prudent, given the possibility of particularly susceptible subgroups in the population and the potential lifetime application of the pharmacological regimen (or its dietary equivalent), should efficacy be demonstrated.

We modified the symptom management/dosage reduction protocol, with full approval by the National Cancer Institute, before the start of CARET: (a) fatigue, hair loss, and loss of appetite were eliminated; bone tenderness along long bones replaced “bone pain,” distinguishing this sign from joint pain usually due to arthritis; (b) “explainable cause” was introduced to allow continuation of dosage when the participant gave acceptable reasons for the symptom, e.g., that weight loss was due to a voluntary dietary regime, or anxiety was associated with unusual stress on the job; and (c) an interval was introduced, if the participant agreed, to see whether the symptom vanished or became nonthreshold during 2 weeks before dosage would be reduced. Most of these quite nonspecific symptoms resolved during this interval and made dosage reduction, replacement of capsules, follow-up calls, and rescheduling of visits unnecessary. Finally, the description of threshold conditions for certain symptoms and signs was modified.

A crucial feature of CARET is the role of continuing pilot phase participants as the Vanguard cohort of CARET (9–11). With a larger cumulative dose, side effects (if any) should appear among Vanguard participants earlier than among those later recruited to CARET. Since the Vanguard cohort is seen twice as frequently and receives more extensive testing and questioning than other CARET participants, the monitoring of toxicity in the subsequently recruited populations in Seattle and in the other study centers was streamlined, making the entire trial more cost effective.

Recruitment to CARET is progressing well; randomization passed the 14,000 mark in January 1993. Efficacy results are expected in 1998.

References


The Carotene and Retinol Efficacy Trial (CARET) to prevent lung cancer in high-risk populations: pilot study with asbestos-exposed workers.


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