Title

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Permalink

https://escholarship.org/uc/item/7g87d317

Journal

Cancer research, 54(7 Suppl)

ISSN

0008-5472

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Publication Date

1994-04-01

Peer reviewed

The β-Carotene and Retinol Efficacy Trial (CARET) for Chemoprevention of Lung Cancer in High Risk Populations: Smokers and Asbestos-exposed Workers[1]

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Abstract

CARET is a multicenter, two-armed, double-masked randomized chemoprevention trial in Seattle, Portland, San Francisco, Baltimore, Connecticut, and Irvine, to test whether oral administration of β-carotene (30 mg/day) plus retinyl palmitate (25,000 IU/day) can decrease the incidence of lung cancer in high risk populations, namely, heavy smokers and asbestos-exposed workers. The intervention combines the antioxidant action of β-carotene and the tumor suppressor mechanism of vitamin A. As of April 30, 1993, CARET had randomized 1,845 participants in the 1985–1988 pilot phase plus 13,260 "efficacy" participants since 1989; of these, 4,000 are asbestos-exposed males and 11,105 are smokers and former smokers (44% female). Accrual is complete everywhere except Irvine, which was the last center added (1991), and the safety profile of the regimen to date has been excellent. With 14,420 smokers, 4,010 asbestos-exposed participants, and 114,100 person-years through February 1998, we expect CARET to be capable of detecting a 23% reduction in lung cancer incidence in the two populations combined and 27, 49, 32, and 35% reductions in the smokers, female smokers, male smokers, and asbestos-exposed subgroups, respectively. CARET is highly complementary to the α-tocopherol-β-carotene study in Finland and the Harvard Physicians Health Study (β-carotene alone) in the National Cancer Institute portfolio of major cancer chemoprevention trials.

Introduction

CARET[3] is a randomized, double-masked, placebo-controlled chemoprevention trial in two groups of adults at high risk for lung cancer: (*a*) men and women age 50–69 years with a history of at least 20 pack-years of cigarette smoking; and (*b*) men age 45–69 years with evidence of extensive occupational exposure to asbestos and a history of cigarette smoking. CARET will evaluate the efficacy and safety of a daily combination of 30 mg of β-carotene plus 25,000 IU of retinyl palmitate (1).

Lung cancer is the leading cause of death from cancer among both men and women in the United States, accounting for approximately 28% of cancer deaths. An estimated 149,000 Americans will die of lung cancers in 1993 (2). Despite aggressive therapy, 5-year survival remains approximately 15%. In recent years, lung cancer incidence has begun to decline among men; however, smoking-related lung cancer incidence has continued to rise among women, surpassing breast cancer in the mid-1980s as the leading cancer cause of death among women. Thus, it is important to study chemoprevention of lung cancer in women as well as men; 44% of the CARET heavy smoker participants are women.

Primary prevention of lung cancer is eminently feasible. The two leading risk factors are well established, namely, cigarette smoking and exposures to respirable fibers of asbestos, which interact synergistically (3–6). Prevention of smoking and smoking cessation have deservedly prominent places in the National Cancer Program plans to reduce age-adjusted cancer death rates (2). Unfortunately, the estimate of smoking prevalence in the United States did not decline in 1991 for the first time in 25 years (7). Occupational exposure standards, protective equipment, and efforts to substitute other materials for asbestos are aimed at primary prevention of asbestos-related cancers.

In combination with those efforts, cancer control strategies aimed at preventing the development or progression of tumors in persons who already have histories of cigarette smoking or occupational exposures to asbestos are essential. Some 29% of men and 25% of women in the 45–64-year age group are current smokers (7) and at least 40% of men and 20% of women ages 45–64 years are former smokers (8). An estimated 4 million workers had significant exposure to asbestos in shipyards and related activities during World War II (9), leading to 4000–6000 excess lung cancer deaths/year currently (9, 10). The latency period offers a major opportunity to intervene to prevent cancers in these high-risk persons.

β-carotene and vitamin A (and its synthetic and naturally occurring analogues, the retinoids) have attracted wide interest as possible chemopreventive agents against lung cancer, based on observational epidemiology and animal studies (Refs. 11–13 and this supplement). In human studies, retinoids have reversed cigarette smoking-induced, preneoplastic bronchial lesions (14) and reduced the incidence of micronuclei in buccal smear cells (15) and sputum cells (16). 13-*cis*-retinoic acid reduced the incidence of second primaries in patients treated successfully for head and neck cancer (17); retinyl palmitate (300,000 IU/day) increased the time to relapse or new primary tumor among patients with stage I lung cancer (18); retinol (25,000 IU/day) reduced the incidence of squamous cell but not basal cell skin cancer in patients with actinic keratosis (19). However, retinol, β-carotene, and 13-*cis*-retinoic acid had no effect on patients with previous skin cancers (19–21), and randomized trials with etretinate and 13-*cis*-retinoic acid had no effect on sputum atypia (22) or biopsy metaplasia (23). These mixed results demonstrate the necessity of randomized, controlled chemoprevention trials in various high risk populations.

Although the exact mechanisms of action are unclear, β-carotene is thought to function as an electron-scavenging antioxidant, and retinol enhances the differentiated state of epithelial cells, including bronchial epithelium, presumably through binding to specific nuclear receptor proteins (the RAR and RXR series) which regulate gene expression, cell differentiation, and proliferation (24). Both β-carotene and retinoids enhance some aspects of the human immune system (25).

Development and Organization of CARET

CARET has been built in steps, as shown in Fig. 1, beginning with two successful pilot studies as part of the Cancer Prevention Research Program of the Fred Hutchinson Cancer Research Center and the

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[3] The abbreviations used are: CARET, β-Carotene and Retinol Efficacy Trial; SEMC, Safety and Endpoints Monitoring Committee.

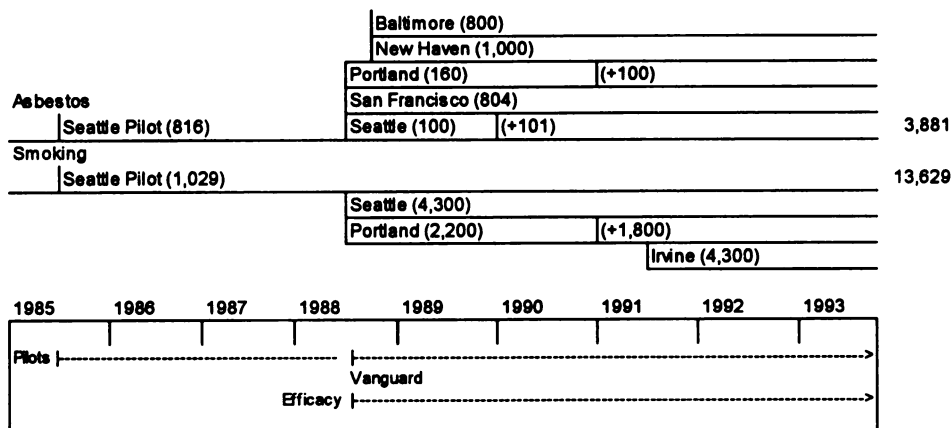Fig. 1. Schema for CARET study centers and accrual goals.

				Baltimore (800)					
				New Haven (1,000)					
Asbestos				Portland (160)	(+100)				
				San Francisco (804)					
Seattle Pilot (816)				Seattle (100)	(+101)				3,881
Smoking									
Seattle Pilot (1,029)									13,629
				Seattle (4,300)					
				Portland (2,200)		(+1,800)			
						Irvine (4,300)			

1985	1986	1987	1988	1989	1990	1991	1992	1993

Pilots |--------------------------------| |-->
                                          Vanguard
                              Efficacy |-->

University of Washington School of Public Health and Community Medicine. The CARET efficacy phase was funded in July 1988 for additional recruitment at the Seattle Study Center and new study centers in Baltimore, New Haven, San Francisco, and Portland. Final expansion began in southern California in mid-1991 at the Irvine Study Center. A steering committee sets CARET policy, reviews progress, approves protocol modifications, and has final approval of publications and any ancillary studies. An external Safety and End-points Monitoring Committee meets with the principal investigator and coordinating center statisticians twice each year to review the semiannual progress report, discuss the progress of the study in detail, and recommend continuation of the study.

Progress of CARET

Pilot Studies and Vanguard. The two CARET pilot studies randomized 1029 current and former smokers and 816 asbestos-exposed workers between June 1985 and August 1988. Male and female smokers recruited via mailings to 29,928 subscribers to King County Medical Blue Shield were randomized in a 2 × 2 factorial trial of 30 mg β-carotene and/or 25,000 IU retinol daily *versus* placebo. Men occupationally exposed to asbestos were recruited from federal and state workers' compensation programs, selected occupational medicine and pulmonary physicians, plaintiffs' attorneys, the Navy Asbestos Medical Surveillance Program, and major unions in the Puget Sound area into a two-arm trial of the combination of 15 mg β-carotene and 25,000 IU retinol daily *versus* placebo. Among asbestos pilot participants, 16% were never smokers and 36% had stopped smoking more than 15 years before enrollment; to recruit a higher risk population, we restricted eligibility criteria for subsequent CARET recruitment to eliminate these two groups.

Participants in both pilots demonstrated good adherence to the daily vitamin regimen, as measured by capsule consumption rates. At 2 years postrandomization, the mean capsule consumption rates were 68% for heavy smokers and 82% for asbestos-exposed workers, with no statistically significant differences between intervention arms. The lower rate for smokers reflected a primary emphasis on toxicity evaluation in that Phase II study such that participants developing monitored symptoms more often had dosage stopped permanently. The only significant difference in monitored symptoms and signs between intervention arms was yellow coloration of the skin, generally mild, with β-carotene. Median β-carotene concentration in the two smoker arms receiving β-carotene increased 12-fold by 4 months and plateaued at that level; for the asbestos active arm (one-half of the dose), the concentrations increased 8-fold. In the retinol-containing arms, median retinyl palmitate values increased 4-fold and serum retinol concentrations increased slightly.

At the end of the two pilot studies, all active pilot participants were asked to continue in the long-term efficacy trial as the vanguard cohort; all who were in active arms in the pilot studies had their dosage changed (where necessary) to 30 mg β-carotene and 25,000 IU retinyl palmitate daily (identical to the CARET efficacy intervention); those on placebo continued on placebo. As of April 30, 1993, 1524 (83%) pilot participants had made the transition and 1239 (81%) of these vanguard participants were still active. All 1845 pilot participants are followed for efficacy end points. Reports on the two pilot studies have been published elsewhere (26, 27).

Recruitment in CARET. Through April 30, 1993, CARET had randomized 4,000 asbestos-exposed workers, exceeding accrual goals at all five CARET asbestos centers, and 11,105 heavy smokers (see Table 1). Randomization of the 13,260 efficacy participants required 874,281 recruitment letters, 33,631 completed screening phone calls, and 17,860 enrollment visits. The yield is low since it was not possible to screen most recruitment lists for smoking-eligible individuals. Seattle and Portland have exceeded their heavy smoker goals, and Irvine is on track to achieve its goal in July 1994; we will complete the recruitment and randomization process for individuals who have received recruitment mailings before the goal is met. After several years of negotiations, we obtained approval in December 1992 from the American Association of Retired Persons to use their mailing list for recruitment of heavy smokers at the CARET study centers, the first research study to obtain such approval.

Randomization. Randomization is based on a permuted blocks algorithm with random block size and equal allocation to the two arms, stratified by study center and exposure population. The unit of randomization is the household to guard against household members taking the wrong vitamin type. Approximately 10% of randomized participants are household members with other CARET participants; the intrahousehold correlation in lung cancer incidence is estimated to be 0.03, based on the observed distribution of lung cancer risk factors in our household pairs and a relative risk of 1.5 for the effect of passive smoking (28). At randomization, a sample of 12.5% of efficacy participants is identified for quality assurance on serum analyses (additional 10 ml blood). An independent 10% sample across all strata is selected to be cohort members of the case-cohort design (29) used for serum analyses.

Participant Characteristics. The coordinating center carefully monitors participant base-line characteristics to ensure the eligibility of participants, check the balance of risk factors between intervention arms, and periodically reassess the sample size requirements based on the participants' risk factors against the CARET design parameters (30). For the combined pilot and efficacy cohorts, the asbestos-exposed and smoker participants have mean ages of 57 and 58,

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Table 1 *CARET recruitment through April 1993 (n = 15,105)*

Study center	No. recruited by year of randomization[a]								Totals	Goals
	1985–1986	1986–1987	1987–1988	1988–1989	1989–1990	1990–1991	1991–1992	1992–1993		
Asbestos-exposed workers										
Baltimore					187	454	165	2	808	800
New Haven					267	385	238	129	1019	1000
Portland					23	98	100	53	274	260
San Francisco					206	291	253	95	845	804
Seattle pilot	190	444	182						816	
Seattle efficacy					14	23	119	82	238	202
Heavy smokers										
Irvine							328	1322	1650	4300
Portland				67	778	1295	998	797	3935	4000[b]
Seattle pilot	378	499	152						1029	
Seattle efficacy				50	1205	690	1456	1081	4482	4300
Asbestos spouses								9[c]	9[c]	60

[a] Years run from July to June to match funding schedule. Pilot recruitment, 1985–1988; efficacy recruitment, 1988 through April 1993.
[b] Portland achieved its goal in June 1993.
[c] Additional recruitment of household members who are smoker-eligible at asbestos study centers (Baltimore, 5; New Haven, 2; San Francisco, 2 thus far).

respectively; 39 and 67% are current smokers; and the mean pack-years are 41 and 49. Of the asbestos-exposed participants, 46% are chest X-ray positive for asbestos-related changes and have a protocol-defined high risk trade work history, while 20% have positive X-ray only and 34% have high risk trade history only. Among those with positive X-rays, 27% are parenchymal positive only, 41% pleural positive only, and 32% both. Mean years from first asbestos exposure to randomization is 35 years.

CARET has been successful in recruiting women; 44% of the total heavy smoker population is female. This is especially noteworthy since women (aged 50–69) are more likely to be never smokers and female smokers smoke less than their male counterparts (7, 8). In the three-county recruitment area for the Seattle Study Center, 46% of the female population aged 50–69 are never smokers compared with 26% of males.[4] Minorities make up about 12% of the asbestos-exposed population and 4% of the smoker population (asbestos: African-American, 8%; Hispanic, 2%; Asian/Pacific Islander, 1%; and other, 2%. Smokers: African-American, 1%; Hispanic, 1%; Asian/Pacific Islander, 1%; and other, 1%). Systematic data on minority representation were not available from any of the recruitment sources used. Relatively high yields from local minority populations were achieved by Baltimore and San Francisco. Portland, Seattle, and Irvine, located in areas with low percentages of age-eligible minorities, mounted extensive efforts to recruit minorities.

Follow-up and Symptom Monitoring. In the first year after randomization, efficacy participants are contacted four times, by telephone at 3 and 9 months and by visits to the study center at 6 and 12 months. In subsequent years, efficacy participants are contacted by telephone at 4 and 8 months past the randomization anniversary date and have an annual visit at the study center. Since effects are likely to depend on the duration of exposure, any side effects of the study vitamins should appear first in the vanguard cohort. The active vanguard group is monitored more closely, with semiannual visits, additional questions on self-report of symptoms, and nonfasting serum analyzed for aspartate aminotransferase, alkaline phosphatase, cholesterol, and triglycerides annually. Development of a symptom exceeding the predefined threshold grade or an increase in hepatic enzyme markers in vanguard participants triggers the CARET symptom management protocol (27). All threshold-grade symptoms are reviewed by the study center principal investigator, as well as all episodes of nonadherence attributed to side effects. Every 6 months, the external SEMC reviews data on the mean grade and proportion of participants

who exceed threshold grades for each monitored symptom and liver function test, and the number of participants becoming inactive due to symptoms, by coded intervention arm.

No consistent clinically or statistically significant excess of any of the 13 monitored symptoms and signs has been observed to date, except mild skin yellowing. As of April 30, 1993, 476 full dose symptom management cases have been completed (132 vanguard and 344 efficacy): 439 resulted in a return to full dose; 25, half-dose, and 12, removal from the study vitamins. There was no significant difference in the distribution of the symptom management cases between intervention arms.

Since we contact CARET participants often and ask detailed questions about symptoms, we conducted a survey of negative or positive impacts on participants in June 1992. About 97% of 400 participants reported liking the phone calls or were neutral; 83% thought we should maintain the present frequency; 56% reported liking the symptom assessment questions in the interviews; 71% thought the content of the symptom questions was just right; and 87% recognized the health-monitoring aspect of the phone calls, which we have reinforced in our multifaceted retention activities.

Smoking Cessation. At each visit after randomization, study center interviewers actively encourage current smokers to quit smoking and former smokers to maintain smoking cessation via referrals and self-help materials. Through April 30, 1993, 29% of the efficacy participants who were current smokers at first visit have accepted smoking cessation packets, 14% of efficacy smokers at baseline reported abstinence at 24 months, while 6% of former smokers have resumed smoking. Our analyses indicate that the effects of smoking cessation on sample size projections are negligible (30).

End Points. All pilot and efficacy participants, including inactive participants, are followed for lung cancer, as well as mesotheliomas, prostate cancers, other cancers, and deaths. Primary sources of initial

Table 2 *Status of CARET participants (as of April 30, 1993)*

	Participants randomized	Active	Alive, inactive	Dead
Pilot (randomized 1985–1988)				
Asbestos exposed	816	568 (70)[a]	167 (20)	81 (10)
Heavy smokers	1,029	671 (65)	259 (25)	99 (10)
Subtotal	1,845	1,239 (67)	426 (23)	180 (10)
Efficacy (randomized 1989–present)				
Asbestos exposed	3,184	2,918 (92)	199 (6)	67 (2)
Heavy smokers	10,076	9,225 (92)	718 (7)	133 (1)
Grand total	15,105	13,382 (89)	1,343 (9)	380 (3)

[a] Numbers in parentheses, percentage.

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[4] Based on unpublished pooled control data from Fred Hutchinson Cancer Research Center case-control studies.

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notices of end points are study participants or their next of kin; secondary sources are state and Surveillance, Epidemiology, and End Results cancer registries in California, Connecticut, Maryland, Pennsylvania, Washington, and Virginia, the Kaiser Permanente patient data base in Portland, state Boards of Health, and the National Death Index. The Endpoints Committee has developed stringent criteria for the ascertainment and review of end point cases. Through April 30, 1993, 360 cancer end point and 228 death end point cases had been closed by the Endpoints Committee, and another 362 reported end points are pending completion of data collection and review. The lung cancer yield is in close agreement with our projections.

Retention: Active Rates and Vitamin Adherence. Retention begins with an informed participant and supportive staff. The CARET quarterly newsletter provides project-specific and general health and social support studies. Side effect fact sheets and letters to personal physicians have been helpful. Mugs, magnets, pins, and certificates of appreciation have been appreciated. Table 2 shows the percentage of randomized participants who were active (alive and receiving study vitamins), alive and inactive, or deceased as of April 30, 1993. Using Kaplan-Meier-type estimates (31), we estimate that at 2 years postrandomization, 93% of alive efficacy asbestos-exposed participants and 90% of heavy smokers are active. The most common reasons for becoming inactive are: unable or unwilling to come to the study center (cited by 32% of inactive efficacy asbestos-exposed participants and 22% of inactive efficacy heavy smoker participants); no interest (23 and 30%, respectively); and development or fear of side effects (31 and 27%, respectively). The pilot participants continue to show high long-term active rates; at 6 years postrandomization, 82% of asbestos-exposed living participants and 78% of heavy smokers are active.

In light of the long duration of CARET, the coordinating center has developed a standardized procedure for approaching inactive participants to encourage them to restart taking study vitamins, except for those few participants for whom capsules were stopped according to the symptom management protocol beginning 6 months after inactivation. As of April 30, 1993, 54 efficacy participants and 90 pilot/vanguard participants have reactivated.

Serum and DNA Bank. Samples are obtained annually on vanguard and biennially on efficacy participants for analysis of serum α- and β-carotene, retinol, and retinyl palmitate and as a resource for appropriate DNA probe analyses.

Design Features and Statistical Power of CARET

CARET End Points

Efficacy. Lung cancer is the primary CARET disease end point. Secondary end points are mesothelioma, all other cancers (except nonmelanoma skin cancers), and deaths. End points are collected on all pilot and efficacy participants. We explored the possibility of conducting ancillary intermediate end point trials within CARET, which would have the advantage of being able to correlate the end point with the "true" end point, lung cancer. However, there are currently no validated intermediate end points for lung cancer. CARET was designed to have 80% power to detect a 23% reduction in lung cancer risk in participants receiving active study vitamins compared with those receiving placebo (30). With 4,010 asbestos-exposed participants and 14,240 heavy smokers, including the anticipated recruitment of approximately 3,135 additional heavy smokers between May 1993 and July 1994, CARET will achieve this target power in year 10, according to current projections. We will conduct exit contacts, conclude follow-up, and close the study centers by mid-1998. With the additional follow-up gained during the closeout period, the power of CARET to detect a 23% reduction in risk will rise to 84%. In addition to the reduction in risk designed for, the sample size/power calculations are most sensitive to four parameters: the lung cancer incidence rate in the placebo arm; the rate of accrual of participants into the trial (see Table 1); the time lag to full effectiveness of the study vitamins; and adherence to taking the intervention agents and refraining from taking supplemental vitamins.

The lung cancer incidence rates for the placebo group are derived from our models (30) which incorporated 1981–1985 Surveillance, Epidemiology, and End Results data on lung cancer incidence by: age and sex; the relative risks for current smokers to never smokers and to former smokers by sex from the American Cancer Society's CPS-II study; distributions of United States population risk factors from the 1985 National Health Interview Survey and the 1986 Adult Use of Tobacco Survey; risk factor distributions of CARET participants; and a relative risk due to asbestos exposure of 3, based on other studies in similar populations (9, 32, 33). As described in the CARET design and monitoring paper (30), the numbers of lung cancers predicted by the model were slightly lower than the number observed in smokers, but higher than the number observed in asbestos-exposed participants, a discrepancy at least partly due to the detection of prevalent tumors by the pre-randomization chest X-ray. We have adjusted the lung cancer rates observed in asbestos-exposed participants downward, which has increased the projected duration of CARET by 0.6 year. We observed 131 actual lung cancers through December 1992 *versus* 128 projected with this adjustment.

Table 3 shows the numbers of person-years of follow-up and of lung cancer end points projected to occur by the conclusion of follow-up in February 1998. For subgroup analyses, CARET will have 80% power to detect a population risk reduction of 35% for the asbestos-exposed population, 27% for the heavy smoker population, 32% for the male heavy smoker population, and 49% for the female heavy smoker population. For secondary end points, CARET has 80% power to detect a population risk reduction of 64% for mesothelioma, 27% for prostate cancer, and 13% for all-cause mortality.

We know of no data directly addressing the time lag to full effectiveness of our study vitamins in preventing lung cancer. We anticipate that the assumption of a 2-year time lag is conservative, given the rapid effect of retinoids on the proportion of buccal mucosal

Table 3 *Projected person-years of follow-up and numbers of lung cancers*

Population and cohort	Active arm			Placebo arm		
	Person-years of follow-up	No. of lung cancers	No. of weighted[a] lung cancers	Person-years of follow-up	No. of lung cancers	No. of weighted lung cancers
Pilot asbestos	4,100	16	15	4,100	20	19
Pilot smokers[b]	8,000	32	29	2,700	13	12
Efficacy asbestos	10,300	68	57	10,200	89	77
Efficacy smokers	37,400	122	100	37,300	157	133
Total[c]	59,800	237	201	54,300	279	240

[a] Weighted by $w(t) = \min(t/y, 1)$, where t is the time since randomization and y is the time lag to full effectiveness (2 years).
[b] Active arm has larger number of person-years, reflecting 3:1 ratio in the pilot heavy smoker group.
[c] Sum of numbers in column may differ from total due to rounding.

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cells with micronuclei in betel nut chewers (15) and on yield of tumors in animals (34).

The sample size/power calculations include estimates of total β-carotene and retinol intake, which we call the medication rate, from both the study vitamins and nondietary sources. For the active arm, we estimate the mean medication rate by the observed capsule consumption rate in the years for which we have data. Projected mean medication rates for future years of the trial are obtained by a linear decline at the average rate seen for the last 2 years for which we have data: 2%/year for pilot participants; 2%/year for efficacy asbestos-exposed participants; and 3%/year for efficacy heavy smokers. Mean capsule consumption rates for efficacy participants have been higher than originally anticipated from the pilot studies experience and data from other trials, 87% at 2 years from randomization for asbestos-exposed participants and 83% for heavy smokers *versus* 80% anticipated. In the placebo arm, we conservatively allow for a linear increase in the mean medication rate from 0% at randomization to 5% at year 3 and then constant for the duration of the trial, reflecting the potential intake of supplementary β-carotene and vitamin A in the placebo group. At randomization, CARET participants agree not to take supplementary β-carotene and to limit supplementary vitamin A to no more than 5500 IU/day. Currently, only 2% of CARET participants are taking some supplementary β-carotene and 1% take over 5500 IU of vitamin A; average doses are far below the study dosage. We do not adjust the trial duration calculations for differences between the arms in dietary intake of β-carotene and retinol but will examine the effect of dietary intake in the analyses planned.

Safety. The vanguard and efficacy cohorts are monitored routinely for 13 symptoms (skin redness, dryness, itching, and yellowing; lip chapping; bone pain; nosebleeds; vomiting; frequency of bowel movements; weight loss; headaches; anxiety; and depression) which can be side effects of β-carotene or vitamin A. These are graded according to the CARET symptom assessment scale. The SEMC and the 1988 National Cancer Institute peer reviewers agreed that any significant side effects can be expected to be identified first in the vanguard cohort. In addition, nonfasting blood samples are obtained annually from vanguard participants for analysis of aspartate aminotransferase, alkaline phosphatase, triglycerides, and total cholesterol. Given the large number of participants, the study has high power to detect a difference between intervention arms in reported side effects and serum analyte concentrations. For example, we will have 99% power to detect whether a 4-year course of supplementation with the CARET study vitamins increases the mean skin redness grade by (as little as) 0.04 on a scale from 0 to 5; the threshold grade which triggers symptom management is 4. All participants are asked at base line and at each follow-up visit if they have been told by a doctor that they have had any of 33 specific health-related conditions (or any other).

Establishing the safety of any chemopreventive agent is essential, especially since participants (and future users) are healthy volunteers without cancers, not patients (35). Even for the high risk participants in CARET, the chance of having lung cancer diagnosed is less than 1/100/year. Thus, it is important to avoid significant side effects, both objective and subjective.

Trial Monitoring

The formal CARET monitoring policy for stopping the trial early due to demonstrated efficacy of the study vitamins is based on O'Brien-Fleming boundaries (35, 36) applied to the weighted number of lung cancer end points. Two interim analyses will be performed at one-third and two-thirds of the projected number of weighted lung cancer end points; the critical P values are 0.0006 for the first interim analysis, 0.015 for the second, and 0.047 for the final analysis. On the basis of experience through April 30, 1993, we project that one-third

of the weighted end points will occur by April 1994 and two-thirds by April 1996. Allowing 6 months for reporting of lung cancer end points cases, we expect to perform the scheduled interim analyses in the falls of 1994 and 1996. At the interim analyses, in addition to the lung cancer end point analyses, the SEMC will integrate differences in overall mortality and other aspects of safety and efficacy in deciding whether both efficacy in preventing lung cancer and safety of the study vitamins have been sufficiently demonstrated to warrant termination of the trial. The SEMC has already decided that, given the nature and intent of CARET, consideration of the lung cancer findings should take precedence over any other efficacy end points that might appear.

In addition to stopping the trial for efficacy, we allow for stopping the trial because no difference is likely to be found between the intervention arms in the incidence of lung cancer. These computations would be performed only at the request of the SEMC or the National Cancer Institute. A stochastic curtailment approach would be used (37) in which the power is computed under the alternative hypothesis of detecting the desired effect at the end of the study, conditional on the data to date. Stopping in the event of low projected power may depend upon other factors, such as the incidence and severity of side effects, costs, and results of other trials. We do not formally test against the alternative hypothesis because the presumed time lag to full effectiveness of the study vitamins implies that the difference between the arms would be less than 23% early in the trial even if the alternative hypothesis is true. By using stochastic curtailment, we can account for the time dependence of the alternative hypothesis.

Analytical Plans

The primary analysis, based on intention to treat, is designed to test for differences between intervention arms in the incidence of lung cancer using a stratified weighted log-rank statistic. The weight function incorporates a linear down-weighting of events occurring in the first 2 years post-randomization to compensate for a time lag to full intervention effect and for undetected cancers that may be present at enrollment.

Secondary analyses of CARET data will include: (*a*) the effect of the CARET regimen on lung cancer incidence in defined subgroups (defined by exposure population, age, and sex); (*b*) the effect of the CARET regimen on the incidence of mesothelioma, prostate cancer, and other cancers and on mortality rates from all causes and from coronary heart disease, both overall and within subgroups; (*c*) the extent to which the effect of CARET agents on lung cancer incidence, incidence of all cancers, and mortality is associated with achieved serum levels, nondietary intake of retinol and β-carotene intake (both from the study vitamins and from supplementary vitamins), and dietary intake of retinol and β-carotene; (*d*) the effect of the CARET regimen on symptoms and signs that are potential side effects of vitamin A or β-carotene; (*e*) the relationship between CARET efficacy end points and base-line factors, such as smoking history, diet, age, sex, occupational history, and spirometric and X-ray findings; and (*f*) the sensitivity of the primary analysis to the choice of weighting for the time to full effect.

Other Analyses and Publications. To further characterize our populations and their experience, both as a cohort of high risk persons and as participants in a major chemoprevention study, we will model lung function (as measured by biennial spirometry) as a function of intervention assignment, time since randomization, cumulative dose, smoking history, dietary factors, age, other medical conditions, X-ray findings, and symptom reports using generalized linear models. We will analyze the effect of long-term supplementation on the serum concentrations of the vitamins, evaluate the changes that have occurred with the transition to vanguard (change in vitamin dose and

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combination and the resultant change in serum concentration of vitamins), and evaluate the relationship to serum retinoid and carotenoid concentrations of participants' characteristics (such as age, sex, smoking, asbestos exposure, and diet).

Analyses planned before the conclusion of CARET include: recruitment and baseline characteristics of CARET participants; recruitment strategies, such as comparison of yields by mailing sources and mailing types, based primarily on the systematically varied experience of the Portland Study Center; early predictors and reasons for participants becoming inactive according to risk factors, behavioral responses, and serum levels; quality assurance in CARET; measures of adherence and retention in long-term prevention studies; longitudinal analyses of the effects of study vitamins on serum triglycerides and vitamin E levels; and use of the household as the unit of randomization.

Additional analyses planned for the completion of follow-up include: problems of intervention adherence in long-term prevention studies; bias in case-control studies in reporting food intake, especially the effect of an untoward event such as diagnosis of cancer on self-reported diet; implications for case-control studies; correlation of lung cancer risk with putative biological markers in stored samples; generalization of findings to populations at risk for lung cancer; relationship between fibrosis at baseline and subsequent lung cancer and total cancer risk in asbestos-exposed individuals; comparison of asbestos-exposed groups across different high risk trades and/or recruitment sources; and effect of intervention assignment on spirometry findings in asbestos-exposed individuals.

Large-scale cancer prevention trials represent major challenges in concept, design, execution, and analysis. CARET is a smoothly functioning, well-managed study with enthusiastic participants and established quality control procedures which have now been adopted by several other large chemopreventive trials. We are on track to achieve by early 1998 the power designed for CARET in the initial 1987 proposal. If β-carotene and retinyl palmitate can give a 23% observed reduction in lung cancer incidence in CARET, that result would extrapolate to a saving of 34,000 lives/year in the United States.

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