*Anti-Cancer Drugs*, 2, pp. 79–86

# CARET, the β-carotene and retinol efficacy trial to prevent lung cancer in asbestos-exposed workers and in smokers

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**CARET is a two-armed, double-blind, randomized chemoprevention trial to test the hypothesis that oral administration of beta-carotene 30 mg/day plus retinyl palmitate 25 000 IU/day will decrease the incidence of lung cancer in high-risk populations: heavy smokers and asbestos-exposed workers who have smoked. The agents combine anti-oxidant and nuclear tumor suppressor mechanisms. Fastidious monitoring for possible side effects is facilitated by inclusion of a Vanguard population. As of 31 December 1990, 6 105 participants of the 18 000 needed have been randomized in the trial. Efficacy results are expected in 1999.**

*Key words:* Asbestos, lung cancer, beta-carotene, retinol.

## Introduction

As has been amply documented, asbestos is an important carcinogenic agent in humans. Occupational exposures to asbestos fibers represent the second leading cause of lung cancer, after cigarette smoking, and the primary cause of mesothelioma of the pleura and peritoneum. Asbestos and cigarette smoke act synergistically in causing lung cancer, but asbestos acts alone in causing mesothelioma.[1–3] Nicholson *et al.* estimated that those workers already exposed to asbestos will suffer asbestos-related cancer deaths at an excess rate of 8000 to 10,000 per year, at least to the end of this century;[4] a consensus figure is 4000 to 6000 excess lung cancer deaths per year.[5]

In the USA, 75% of men and 50% of women in the age group 55–64 years are current or former smokers,[6] and several million workers have been exposed to asbestos.[4] The latency period between exposure to either of these carcinogens and development of lung cancer may be decades. Thus, a chemopreventive agent for lung cancer could save many lives even though the exposure occurred and ceased years earlier. Even though the relative risk does decline, of course, compared with continuing smokers or with never-smokers, the accumulated increase in risk of lung cancer probably does not decline after smoking ceases.[7]

The rationale for cancer chemoprevention programs is based on interrupting late stages of promotion and progression in the multi-stage process of carcinogenesis. Such actions are exactly what is needed for high-risk individuals, especially smokers or former smokers who are workers or retired workers with significant occupational exposures to asbestos. Thus, chemoprevention would be complementary to primary prevention —avoiding or ceasing cigarette smoking and reducing or eliminating asbestos exposures.

Among the multiple classes of chemicals with apparent chemopreventive activity,[8–10] vitamin A

This project is supported by grant CA 34847 from the National Cancer Institute.

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(retinol) and β-carotene are leading candidates for efficacy in humans. Since 1967 it has been known that vitamin A can markedly reduce the incidence of squamous metaplasia and tracheobronchial tumors in rats,[11] a finding confirmed many times with various naturally occurring and synthetic retinoids in several animal species. Most importantly, some animal studies have demonstrated that substantial reductions in tumor incidence and tumor size can be obtained when the retinoids are administered long after the exposures to inducing carcinogens. For example, retinyl acetate decreased the incidence of mammary cancers at 20 weeks by about 50% when given to rats for a 6-week period starting 2 weeks prior to dimethylbenzanthracene (DMBA); starting 12 weeks after exposure to DMBA, there was still a 40% decrease in incidence of mammary tumors at 20 weeks.[12] Organ culture experiments have demonstrated that retinyl methyl ether can inhibit the metaplastic transformation induced by crocidolite or amosite asbestos in hamster tracheal cells,[13] and similarly reverse metaplasia induced by 3,4-benzpyrene or by cigarette smoke condensate.[14]

Epidemiologic investigations in humans generally have shown a striking inverse relationship between intake of β-carotene and/or vitamin A-rich foods and lung cancer risk,[15–19] and between serum concentrations and lung cancer risk.[20–24] To estimate the potential benefit of dietary supplementation with β-carotene/retinol on lung cancer risk, Byers *et al.*[24,25] reviewed seven epidemiologic studies. Compared with subjects in the lowest quartile or quintile of intake, subjects in the highest category of intake had an average relative risk for lung cancer of 0.59. Epidemiologic associations do not establish that increasing the intake or blood concentrations of vitamin A and β-carotene would actually decrease the incidence of lung cancers. Only intervention studies can address that crucial question.

Retinoids have reversed cigarette-smoking preneoplastic bronchial lesions and reduced the incidence of micronuclei in buccal smear cells. Mathe *et al.*[26] in France administered etretinate, a synthetic retinoid, for 6 months at 30 mg/day to 67 heavy smokers who underwent serial bronchoscopies with biopsies. In the 34 subjects with severe metaplasia at the start of the study, treatment significantly decreased the degree of metaplasia. In studies by Stich *et al.* among betel nut chewers in the Philippines,[27] the proportion of buccal mucosal cells with micronuclei (an indicator of nuclear chromatin damage) decreased to normal during 3 months of treatment with the combination of retinol and β-carotene. The micronuclei reappeared promptly upon stopping the treatment in these betel nut chewers.

Three potentially definitive clinical chemoprevention trials are underway, supported by the U.S. National Cancer Institute. In addition to CARET (described below), these are the Harvard Physicians Study, initiated to assess the effect of aspirin on heart disease and continued to ascertain the effect of β-carotene on overall cancer incidence, and the Alpha Tocopherol–Beta Carotene Study (ATBC) in 29,000 smokers in Finland, testing β-carotene plus vitamin E for chemoprevention of lung cancer.

Subjects in chemoprevention trials are healthy volunteers without cancers, not patients, who might tolerate considerable discomfort or risk. Since the risk of lung cancer, even among high-risk asbestos-exposed smokers, is of the order of one in a hundred per year, it is essential that a chemopreventive regimen be demonstrated to have no major objective or subjective side effects.

## The design of CARET

CARET is a two-armed, double-blind, randomized chemoprevention trial to test the hypothesis that oral administration of β-carotene 30 mg/day plus retinol 25,000 IU/day will decrease the incidence of lung cancer in heavy smokers and asbestos-exposed workers who have smoked.

The presumed mechanisms of action are attractive. β-Carotene is thought to function as an electron scavenging anti-oxidant[28,29] and as a precursor of retinol. Retinol functions to maintain the differential state of epithelial cells, including those in the bronchial epithelium.[28,29] Retinol *in vitro* inhibits cell growth, possibly via changes in cell surface glycolipids and glycoproteins.[30,31] Retinol and retinoic acid may exert such actions through binding to specific proteins in the cell nucleus, proteins which then regulate gene expression. Genes coding for retinoic acid binding proteins have been localized to the short arm of chromosome 3 and to the long arm of chromosome 17;[32–34] chromosome 3p is known to have three or more 'tumor suppressor' genes with gene products yet to be identified. Blomhoff *et al.* have demonstrated the uptake of retinol bound to retinol-binding protein and of retinoic acid esters bound to chylomicron remnants into myeloid leukemic cells via low-density lipoprotein receptors; these authors have emphasized the

**Table 1.** Eligibility criteria for CARET

| |
|---|
| *Asbestos workers* |
| Age 45–69 years, men |
| Current cigarette smoker or ex-smoker (quit ≤ 15 years ago) |
| Extensive occuptational exposure |
| ≥ 15 years since first occupational exposure |
| Chest X-ray positive in ILO criteria and/or ≥ 5 years in high-risk trade completed ≥ 10 years ago |
| *Smokers* |
| Age 50–69 years, men and women |
| Cigarette smoking history of ≥ 20 pack years |
| Current smoker or ex-smoker (quit ≤ 6 years ago) |
| *Exclusions* |
| History of cancer within 5 years |
| History of liver disease within 12 months |
| SGOT or alkaline phosphatase greater than 2.5× and 1.5× 95th percentile of normal, respectively |
| Vitamin A supplementation >5500 IU/day |
| β-Carotene supplementation |
| Pre-menopausal status |

greater margin of safety for retinol compared with retinoic acid.[35]

The CARET study population is composed of two groups of participants: the Vanguard group of continuing participants who were enrolled in the CARET pilot studies during 1985–88, and the Efficacy group of participants recruited in five co-operating centers since 1989. The eligibility criteria for CARET are shown in Table 1.

The criteria for smokers are straightforward. The eligibility criteria for the asbestos-exposed workers require definition. The occupational exposure is defined by job titles, plus work for the required length of time in one or more of eight defined high-risk jobs, and/or chest X-ray with changes compatible with asbestos-induced pulmonary (pleural or parenchymal) disease. The high-risk trades from which we have recruited in Seattle and are now recruiting elsewhere are listed in Table 2. We have had to develop a dictionary of high-risk trades to accommodate different terminology in different parts of the country; yet other terms might be synonymous in other countries. In addition, we have not been recruiting miners, textile workers, cement product makers, or certain other job-related groups that have been studied by other research groups around the world.

**Table 2.** List of high-risk trades

| Seattle term | Synonyms at other CARET study centers |
|---|---|
| Asbestos worker | Insulator/lagger |
| Shipyard boilermaker | Shipyard welder/machinist/coppersmith |
| Plasterboard worker | Dry waller/plasterer/lather/taper |
| Shipyard electrician | Electrical worker (NH shipyards only) |
| Plumber/pipefitter | Steamfitter/refrigeration worker |
| Shipscaler | Shipyard laborer (NH) |
| Shipfitter | Rigger |
| Sheetmetal worker | Same |

Pilot studies during 1985–88 identified dosage ranges of retinol and β-carotene that substantially increase serum carotene and retinyl palmitate concentrations without producing signs of liver toxicity, markedly elevating triglycerides, or increasing the prevalence of any relevant symptom or sign (except mild yellowing of the skin among those on β-carotene) under a fastidious symptom assessment protocol[36,37] (see Table 5).

The smokers pilot study had four arms that made a 2 × 2 factorial design composed of retinol (25,000 IU/day) and β-carotene (30 mg/day). In the transition to CARET, the participants on the three active treatments were assigned to the active CARET regimen, and the placebo group continued to receive placebo. The asbestos-exposed workers pilot had begun as a two-armed study (placebos vs retinol 25,000 IU/day plus β-carotene 15 mg/day). These participants remained on their originally assigned treatments, but the β-carotene dose was increased to 30 mg/day.

The recruitment to the pilot studies was carried out under eligibility criteria that were identical to those above for CARET for smokers, but men as old as 74 years were eligible for the asbestos-exposed pilot cohort and asbestos-exposed individuals did not have a cigarette smoking eligibility requirement. We learned that 16% of our pilot asbestos-exposed population were never-smokers, 62% ex-smokers (some a long time), and only 22% current smokers.

During 1985–88, 816 men were randomized (target 800) in the asbestos-exposed cohort, yielding 1300 person-years of observation during the pilot; 1029 men and women were randomized in the smokers pilot (target 920), yielding 1750 person-years of observation. Recruitment of smokers was drawn from local health insurer rolls. Recruitment of the asbestos-exposed cohort involved federal and state workers' compensation programs, selected occupational medicine and pulmonary physicians, plaintiffs' attorneys, the major unions in the Seattle area, and the US Navy Asbestos Medical Surveillance Program at Bremerton, Washington. The active participants

averaged better than 90% adherence to taking their study vitamins. Including dropouts, adherence at 3 years after randomization was 80% in the asbestos-exposed workers cohort.

A crucial design feature of CARET is that the participants in the pilot studies continue in CARET as the Vanguard population. They accumulated many person-years of treatment prior to beginning the accrual of the Efficacy population. Thus, the Vanguard participants should reveal any toxicity problems due to cumulative dose of vitamin A and/or β-carotene before such problems may be encountered in the Efficacy participants.

Extensive assumptions are required to calculate the sample size to achieve a desired power. The CARET asumptions are shown in Table 3. Several of these parameters require explanation. Values have been chosen based on review of the relevant literature and specific assumptions. For some of the parameters, periodic revisions are being made as our field experience allows us to refine the projections.

**Table 3.** Study design parameters

| | |
|---|---|
| Annual incidence of lung cancer in placebo group (from 1st to 8th year after randomization) (1st year–8th year) | |
| Smokers | 0.003–0.006 |
| Asbestos Vanguard (includes never-smokers) | 0.006–0.011 |
| Asbestos efficacy | 0.008–0.013 |
| Maximal potential chemopreventive effect | 33% reduction in lung cancer incidence |
| Time lag for full effect | 2 years |
| Accrual period | |
| Vanguard (completed) | 3 years |
| Efficacy | 5 years |
| Length of study | 10 years (from start of funding, 1988) |
| Overall adherence to medication schedule | |
| Vitamins: smokers | 100% at randomization<br>67% at 3 years<br>62% at 8 years |
| Vitamins: asbestos | 100% at randomization<br>80% at 3 years<br>75% at 8 years |
| Placebo groups: smokers and asbestos | 0% at randomization<br>5% at 3 years<br>5% at 8 years |
| Incidence of death from causes other than lung cancer (from 1st to 8th year) | |
| Smokers | 0.015–0.025 |
| Asbestos | 0.019–0.026 |
| Loss to follow-up | 2% over full study |
| Statistical testing procedures | |
| Level | 0.05, 2-sided |
| Power | 80% |
| Procedure | Weighted log-rank test |

The baseline risks of lung cancer in the participant population are affected by age, sex, and smoking history; these factors are monitored for their effect on the power of the study. We estimated the lung cancer incidence rates from four pieces of information: (1) the 1984 incidence in the US by age from SEER registries; (2) relative risks associated with smoking and asbestos-exposure variables; (3) distribution of these variables in the US population; and (4) distribution of these variables in our pilot population. The first three parameters allow us to estimate the lung cancer incidence rates in a population of never-smokers; the fourth then allows us to estimate the incidence rates in our study population. Thus, we estimated the lung cancer incidence rate for asbestos-exposed participants to be 1.2 per 100 person-years, based on (1) the 1984 rate of 0.23 lung cancers per year per 100 males of 45–69 years of age; (2) a relative risk due to asbestos exposure in our highly exposed subjects of 3;[2,4,38] and (3) an estimated relative risk of 15 for average smoking history in current and former smokers,[39] adjusted for years since cessation.[7]

Note in Table 3 that we calculate expected lung cancer incidence separately for asbestos-exposed workers recruited under pilot study eligibility smoking criteria and under CARET eligibility criteria.

Support for this estimate comes from review of the Selikoff-Hammond studies of US insulators, in which the observed lung cancer incidence rate among workers with 20+ years since first exposure to asbestos was 1.1 per 100 persons per year.[40] Mean age in the Seattle recruitment was 59 years, while the insulator subgroup's mean age was only 49 years, an age difference associated with a 3-fold higher risk according to SEER data. Conversely, the insulators had higher asbestos exposures and higher current smoking prevalence.

For public health purposes, a sizeable reduction in lung cancer risk is needed to justify a general intervention program. Thus, we designed CARET to have 80% power to detect an efficacy corresponding to a maximal chemopreventive effect of 33% reduction of lung cancer incidence in a fully compliant population of the two high-risk groups combined and/or, secondarily, 50% reductions in each subgroup alone. Such major effects may be feasible, based upon reductions of that magnitude observed in animals,

the prompt effects on micronucleus formation and on bronchial biopsies in humans, and the 2- to 5-fold variation in lung cancer risk between extreme quintiles or quartiles of β-carotene/vitamin A intake or blood levels. Other parameters listed in Table 3 diminish the actual reductions that can be observed from a maximal potential reduction of 33% to a projected actual reduction of 22% (see Table 6).

We have used a time lag of 2 years to full effect from the intervention, with a linear relationship from zero to full effect. The lag time to full effect adjusts somewhat for undetected cancers that may be present at randomization. We know from studies of serial chest radiographs that lung cancers generally grow rapidly once they are detected radiographically; 3-month intervals were too long for clinically useful detection for treatment.[41,42] We have documented marked increases in circulating β-carotene and retinyl palmitate. Finally, we know that similar doses of vitamin A and β-carotene achieve chemopreventive effects within weeks in animal studies, *in vitro* studies, and human intermediate endpoint studies.

Assumptions about years for accrual, mean follow-up, and overall duration of the study have to be adjusted as experience is gained at the co-operating study centers listed in Table 4, and as the final recruitment site is activated in Irvine, California (planned for April 1991). So long as attrition is low and medication rate is high, extension of the follow-up would increase power.

The medication rate is the average fraction of full dose taken. The power of the study will be diluted either by participants in the placebo arm taking active agents on their own (a serious possibility with all the current publicity about β-carotene and vitamin A and inclusion of these agents in multivitamins) or participants in the active treatment arm failing to take their capsules (including those who become inactive, or are removed from dosage under our symptom management protocol). The estimates here are based upon actual results of 7-year 0.63 medication rate and 0.73 adherence rate in the Lipid Research Clinics trial, 0.80 medication rate over 3 years in the aspirin trial, 0.85 adherence at 27 months in the β-blocker trial,[43–45] and 0.82 medication rate at 36 months for the CARET asbestos-exposed workers pilot cohort (now Vanguard). The estimation of loss to competing risks is based upon actuarial estimates and experience from other long-term intervention trials.[43–45] We have allowed for higher loss among the asbestos-exposed cohort than among the smokers, mostly due to inclusion of women in the smokers cohort.

In sum, with these parameters, a two-sided $\alpha$ 0.05 test using a modified log-rank test statistic down-weighted over 2 years, and power of 0.80, over 4000 asbestos-exposed workers and over 13,000 smokers are needed, as listed in Table 4 by study center.

The key to the success of CARET will be the attainment of its recruitment goals, and then retention of those randomized subjects. Each center has established its own goals for recruitment which must be attained for the successful completion of the study.

## Enrollment and follow-up

We obtain considerable baseline history and, for the asbestos-exposed cohort, chest X-ray for routine and International Labor Organization (ILO) interpretation at the first visit. Spirometry is done at both the first visit and the second visit (randomization visit). We utilize a 3-month enrollment period between these two visits, with all participants on placebo, to assess initial compliance

**Table 4.** Study center recruitment goals and progress

| Study center | Asbestos goal | Smoking goal | Total goal | Randomized as of 31 Dec 1990 |
|---|---|---|---|---|
| Baltimore | 800 | 0 | 800 | 402 |
| New Haven | 1 000 | 0 | 1 000 | 433 |
| Portland | 660 | 4 000 | 4 660 | 1 402 |
| San Francisco | 800 | 0 | 800 | 379 |
| Seattle: Vanguard | 816 | 1 029 | 1 845 | 1 845 |
| Efficacy | 201 | 4 300 | 4 501 | 1 644 |
| Irvine (start in 1991) | 0 | 4 300 | 4 300 | 0 |
| Total | 4 277 | 13 629 | 17 906 | 6 105 |

and to obtain laboratory and chest X-ray results before randomizing any participant. During the next 12 months we have contact with the participants every 3 months, alternately by phone call and by clinic visit; in subsequent years, clinic visits are annual and phone calls occur at the 4 and 8 month mark of each year. Vanguard participants are seen twice each year, in addition to the two phone calls, as part of their sentinel function about possible toxicity related to cumulative dose.

Our monitoring for possible side effects of the vitamin regimen includes the process outlined in Table 5. The goal is to keep each participant taking as close to the full study dose as possible without experiencing any untoward effects.

Participants are followed until a primary or secondary endpoint is reached or the study is completed, which is projected for 1998. The primary endpoints are diagnoses of lung cancer or mesothelioma. The secondary endpoints are other malignancies and deaths from all causes. The expected numbers of primary endpoints are shown in Table 6.

A well-defined process for evaluating endpoints has been implemented. Each presumed primary endpoint is reviewed by the coordinating center pathologist. The pathologist's assessment and other pertinent data are then reviewed independently by two physician members of the CARET Endpoints Committee. The review classifies the basis for the confirmation of cancer, and the contribution of cancer to the death of the participant. In cases of disagreement, the Endpoints Committee Chair decides or brings the case for discussion to the Committee, according to specific criteria.

The primary analysis is the incidence of lung cancer in the two high-risk populations, comparing treatment arm against placebo arm. Secondary analyses will look at the effect of explanatory variables such as age, sex, smoking history, threshold grade symptoms and signs, side-effects management reports, compliance estimates, individual medication rates, and endpoint data, plus occupational asbestos exposure history, chest radiograph ILO interpretation, and periodic spirometry test results for the asbestos-exposed population. Ancillary analyses of interest include potential efficacy against mesothelioma or other cancer sites, causes of death, role of smoking in fibrosis and role of fibrosis as an independent risk factor in lung cancer among the asbestos-exposed cohort, variation in serum β-carotene response among participants on similar administered doses, smoking cessation success, and behavioral aspects of participation and compliance.

**Table 5.** Monitoring for potential side effects

Self-reports of symptoms and signs:
- symptom assessment questionnaire administered every 4 months
- symptoms graded on a standardized scale

Physical examination for signs:
- physical examination every 12 months
- signs graded on a standardized scale

Symptoms and signs monitored:

| Symptoms | Signs |
|---|---|
| headaches | skin redness, rash |
| anxiety | skin dryness |
| depression | skin itching |
| vomiting | skin yellowing |
| bowel movements | dryness of lips |
| nosebleeds | bone tenderness |
| weight loss | |
| bone pain | |

Any signs or symptoms that persist for 2 weeks and reach a pre-determined threshold grade are managed by a standard drug challenge approach. The sequence of steps is:

- withdrawal of study vitamins
- re-challenge at full dose if symptoms resolve
- withdrawal of study vitamins if symptoms recur on re-challenge
- re-challenge at half dose if symptoms resolve
- withdrawal of study vitamins if symptoms recur on half dose re-challenge

**Table 6.** Expected number of weighted lung cancer cases by study arm

| | No. of lung cancer cases | Arm | % Change |
|---|---|---|---|
| Efficacy asbestos | 97 | P | −22 |
| | 76 | BC/R | |
| Efficacy heavy smokers | 152 | P | −22 |
| | 118 | BC/R | |
| Vanguard asbestos | 31 | P | −23 |
| | 24 | BC/R | |
| Vanguard heavy smokers (3/4th in BC/R arm) (see text) | 13 | P | −20 |
| | 32 | BC/R | |
| Total | 293 | P | −22 |
| | 250 | BC/R | |

P, placebo; BC/R, β-carotene 30 mg and retinol 25,000 IU/day.

## Conclusion

Several lines of research suggest that β-carotene and/or retinol could be effective and safe

chemopreventive agents against lung cancer. Currently three large trials are underway.

The study reported here, CARET, evolved from successful pilots. It is unique in that its study participant group consists of both smokers and asbestos-exposed workers, and in that its regimen is a combination of β-carotene and vitamin A.

Experience with prevention trials has revealed some important differences in their design and conduct from treatment studies. These differences include the problems of recruiting very large numbers of participants from populations not experiencing current illness and maintaining them on the study treatment for long periods of time while monitoring to protect them against side effects. Participants in prevention trials are partners in research; they are not patients. In addition, there are major challenges managing the people, the data, and the specimens for this scale of operation.

We expect CARET, combined with the results of the other two major trials, to determine by the end of the decade whether vitamin A and β-carotene can be recommended to occupationally defined high-risk groups and to the public as effective chemopreventive agents against lung cancer.

## Acknowledgments

The authors wish to acknowledge the key roles of Study Center and Coordinating Center staff and Study Managers.

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*(Received 8 January 1991; accepted 8 January 1991)*