Alerts, Notices, and Case Reports

Recruitment for the β-Carotene and Retinol Efficacy Trial (CARET) to Prevent Lung Cancer in Smokers and Asbestos-Exposed Workers

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THERE ARE THREE major lung cancer chemoprevention trials under way worldwide. One, the β-Carotene and Retinol Efficacy Trial (CARET), is recruiting subjects primarily in California, Oregon, and Washington. Our purpose in this article is to share information about the design of CARET and the recruitment strategy and to address some questions physicians may raise about their patients who participate in CARET. The investigators welcome referrals to the CARET study centers in Irvine, San Francisco-Vallejo-Santa Clara, Portland, and Seattle (as well as Baltimore and New Haven).

Lung cancer is the number one cancer killer of both men and women in the United States and in an increasing number of other countries. Lung cancers account for 27% of all cancer deaths and 6% of total deaths in the United States, an estimated 143,000 deaths in 1991.[1] Despite aggressive efforts at early diagnosis and multimodality therapy, the five-year survival rate from lung cancers remains miserably low, about 15%.[2] Unlike most common cancers, the causes of lung cancer are well established.[3-5] Thus the National Cancer Institute has placed highest priority on the prevention of lung cancer. Primary prevention requires preventing the initiation of cigarette smoking, assisting cessation of smoking, and protecting people from exposures to asbestos, radon, arsenic, and a few other known pulmonary chemical carcinogens.

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For tens of millions of Americans who have already incurred decades of cigarette smoking exposure and several million Americans who have had considerable occupational exposures to asbestos, especially in West Coast seaports, so-called secondary prevention is essential to overcoming the risk factors already at work. About 75% of men and 50% of women between 55 and 64 years of age are current or former smokers.[6] Without secondary prevention, the increased risk of lung cancer does not decline in former smokers after smoking ceases, even though the relative risks do decline compared with continuing smokers or with persons who have never smoked.[7] Among workers already exposed to asbestos, 4,000 to 6,000 are projected to die of lung cancer per year at least until the year 2000 and up to 8,000 to 10,000 will die of all asbestos-related cancers per year.[8,9]

The rationale for cancer chemoprevention programs is based on interrupting late stages of promotion and progression in the multistage process of carcinogenesis. Such actions are exactly what is needed for high-risk persons to take advantage of the latent period (or "time bomb") of 20 to 40 years between first exposure and peak risk for lung cancer. Among the multiple classes of chemicals with apparent chemopreventive activity, vitamin A (retinol) and β-carotene are leading candidates for efficacy in human beings.[10-12] As described elsewhere, studies in animals, epidemiologic analyses, cell culture experiments, and short-term clinical trials to reverse bronchial metaplasia or buccal mucosa cell micronuclei have laid a strong foundation for direct intervention trials.[13]

Three potentially definitive clinical chemoprevention trials, supported by the US National Cancer Institute, are under way. The Harvard Physicians Study, which was initiated to assess the effect of aspirin on heart disease, was continued to ascertain the effect of β-carotene on overall cancer incidence in 22,000 physicians. The α-Tocopherol–β-Carotene Study was established to test the combination of β-carotene plus vitamin E in the chemoprevention of lung cancer in 29,000 smokers in Finland. Finally, the CARET trial was designed to test the combination of β-carotene and vitamin A in 18,000 smokers and asbestos-exposed workers. The design and recruitment strategy for CARET are described herein.

Subjects in chemoprevention trials are healthy volunteers without cancer, not patients who might tolerate considerable discomfort or risk. Because the risk of lung cancer, even among high-risk asbestos-exposed smokers, is on the order of 1 per 100 per year, it is essential that a chemopreventive regimen be shown to have no major objective or subjective side effects.

Design of CARET

CARET is a two-armed, double-blind, randomized chemoprevention trial to test the hypothesis that the oral administration of β-carotene, 30 mg per day, plus retinol, 25,000 IU per day, will decrease the incidence of lung cancer in heavy smokers and asbestos-exposed workers who have smoked.[14,15]

Choice of Agents

The presumed mechanisms of action of β-carotene and of vitamin A (retinol) are attractive and complementary. β-Car-

ABBREVIATIONS USED IN TEXT

CARET = β-Carotene and Retinol Efficacy Trial
ILO = International Labour Office

otene is an electron-scavenging antioxidant as well as a precursor of retinol. Retinol functions to maintain the differentiated state of epithelial cells, including those in the bronchial epithelium, and inhibits cell growth.[16-18] Retinol and retinoic acid bind to specific proteins in the cell nucleus that then regulate gene expression, probably including tumor suppressor mechanisms. A virtue of these agents is the low expected incidence of untoward effects from the dosages prescribed.

Study Population

The study population consists of two groups of participants, the Vanguard group of continuing participants who were enrolled in the CARET pilot studies during 1985 to 1988 in Seattle, and the Efficacy group of participants whose recruitment in the six cooperating study centers began in 1989. The eligibility criteria for CARET are summarized in Table 1.

TABLE 1.—*Eligibility Criteria for CARET*

Asbestos Workers
Age 45-69 yr, men
Current cigarette smoker or ex-smoker (quit ≤ 15 yr ago)
Extensive occupational exposure
≥ 15 yr since first occupational exposure
Chest x-ray film positive by ILO criteria and/or ≥ 5 yr in high-risk trade completed ≥ 10 yr ago
Smokers
Age 50-69 yr, men and women
Cigarette smoking history of ≥ 20 pack yr
Current smoker or ex-smoker (quit ≤ 6 yr ago)
Exclusions
History of cancer within 5 yr
History of liver disease within 12 mo
SGOT or alkaline phosphatase > 2.5× and 1.5× 95th percentile of normal, respectively
Vitamin A supplementation > 5,500 IU/d
β-Carotene supplementation
Premenopausal status

ILO = International Labour Office
SGOT = serum aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)

The pilot studies identified dosage ranges of retinol and β-carotene that substantially increase serum concentrations of carotene and retinyl palmitate without producing signs of liver toxicity, elevating serum triglycerides substantially, or increasing the prevalence of any relevant symptom or sign (except mild yellowing of the skin among those receiving β-carotene) under a fastidious protocol for assessing symptoms (Table 2).[13] A crucial design feature of CARET is that the 1,029 smokers and 816 asbestos-exposed participants in the pilot studies continue in CARET as the Vanguard population. They accumulated 3,000 person-years of treatment before we began the accrual of the Efficacy population in 1989. The Vanguard participants should reveal any toxicity problems resulting from the cumulative dose of vitamin A, β-carotene, or both, before such problems are encountered in the Efficacy participants.

Smoker participants, both men and women, are recruited primarily from the rolls of various health insurers and health maintenance organizations. The pilot study of smokers had

TABLE 2.—*Monitoring for Potential Side Effects**

Method
Self-reported symptoms and signs: symptom assessment questionnaire administered every 4 mo; symptoms graded on a standardized scale
Physical examination for signs every 12 mo; graded on a standardized scale
Laboratory tests: SGOT, serum alkaline phosphatase
Monitoring of symptoms: anxiety, depression, headaches, bowel movements, nosebleeds, vomiting, weight loss
Monitoring of signs: bone pain, dryness of lips, skin dryness, itching, redness or rash, or yellowing

SGOT = serum aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)

*Any signs or symptoms that persist for 2 wk and reach a predetermined threshold grade are managed by a standard drug challenge approach. The sequence of steps is withdrawal of study vitamins; rechallenge at full dose if symptoms resolve; withdrawal of study vitamins if symptoms recur on rechallenge; rechallenge at half dose if symptoms resolve; and withdrawal of study vitamins if symptoms recur on half dose rechallenge.

four arms (regimens): retinol (25,000 IU per day) plus β-carotene (30 mg per day), each agent alone, and placebos. In the transition to CARET, the participants in the three active treatments were assigned to the active CARET regimen and the placebo group continued to receive placebo. The asbestos-exposed workers were recruited from occupational and pulmonary physicians' practices, federal and state workers' compensation programs, labor unions in the Seattle-Puget Sound area, plaintiffs' attorneys, and the Navy Medical Asbestos Surveillance Program in Bremerton, Washington. The pilot study of the asbestos group began as a two-armed study (placebos versus retinol, 25,000 IU per day, plus β-carotene, 15 mg per day). These participants receive their originally assigned treatments, but the β-carotene dosage was increased to 30 mg per day. Acceptance of the treatment regimen is high, and adherence to dose is more than 90% among active participants.

Extensive assumptions are required to calculate the sample size to achieve a desired statistical power in these kinds of prevention trials.[13,15] The key parameters are the annual incidence of lung cancer in the placebo group after randomization, the greatest potential chemopreventive effect of the intervention, the time lag until full effect, the adherence to the medication schedule, the accrual period, the length of follow-up, the incidence of death from causes other than lung cancer, the loss to follow-up, and the statistical requirements.

For public health purposes, a sizable reduction in the risk of lung cancer is needed to justify a general intervention program. Thus we designed CARET to have 80% power to detect an efficacy corresponding to a maximum chemopreventive effect of 33% reduction in incidence of lung cancer in a fully compliant population of the two high-risk groups combined and, secondarily, 50% reductions in each subgroup alone. Such effects may be feasible, based on the reductions of that magnitude observed in animals, the prompt effects on micronucleus formation and human bronchial biopsy specimens, and the two- to fivefold variation in risk of lung cancer between extreme quintiles or quartiles of β-carotene–vitamin A intake or blood levels.

Imperfect adherence, time lag until full chemopreventive effect, and competing causes of death diminish the observable reductions from 33% to a projected actual reduction of 22%. We down-weight cases of lung cancer that occur within the first two years (linear approach to full preventive effect at two years) to adjust for undetected cancers that may be

present at the time of randomization. We know from studies of serial chest radiographs that most lung cancers grow rapidly once they are detected radiographically; chest roentgenograms at three-month intervals failed to improve clinical outcomes.[19,20] Finally, we know that chemopreventive effects of vitamin A and β-carotene can be observed within several weeks in animal studies, in in vitro studies, and in human intermediate end-point studies. We document marked increases in circulating levels of β-carotene and retinyl palmitate.

The medication rate, a quantification of adherence, is the average fraction of full dose taken. The power of the study will be diluted by participants in the placebo arm taking active agents on their own (especially with all the current publicity about β-carotene and vitamin A and inclusion of these agents in multivitamins) and by participants in the active treatment arm failing to take their capsules—including those who become inactive or are removed from the regimen under our symptom management protocol.

Estimation of loss to competing causes of death is based on actuarial estimates; we allow for higher loss among the asbestos-exposed cohort than among the smokers, mostly because women constitute half of the smokers. We refine sample size and follow-up projections as we accumulate experience with risk factor (age, sex, smoking history), accrual, and adherence data. As long as the attrition is low and the medication rate is high, extension of the follow-up would increase the power.

In summary, using a two-sided test, α .05, with a modified log-rank test statistic down-weighting lung cancer cases occurring during the first two years, we estimate that 4,300 asbestos-exposed workers and 13,600 smokers and former smokers are needed to have a power of .80 (80% probability of detecting a true effect) if follow-up is an average of 6.5 years.[13,15] We project 293 weighted lung cancer cases in the placebo arm and 250 cases in the treatment arm, if the greatest potential chemopreventive efficacy is, indeed, 33%.

Enrollment and Follow-up

Recruitment Goals

The keys to the success of CARET will be to attain the recruitment goals at each study center (Table 3) and then to retain these subjects. The West Coast study centers aim to recruit many additional participants, especially the Irvine center, which was funded in mid-1991.

Contact Schedule

At the first visit, baseline history is obtained. In the asbestos-exposed cohort, a chest roentgenogram for routine and International Labour Office (ILO) interpretations is obtained at the first visit and spirometric measurements at the first and second (randomization) visits. A report is prepared for the participant's personal physician. We use a three-month enrollment period with all participants receiving placebo to assess initial compliance and to obtain laboratory and chest roentgenographic results for determining eligibility before randomization. During the next 12 months we contact the participants every 3 months, alternately by telephone and clinic visit; in subsequent years, clinic visits are annual, with follow-up by telephone at the 4- and 8-month marks of each year. Vanguard participants are seen twice a year, in addition to the two telephone calls, because they serve a sentinel function for detecting possible toxicity related to cumulative dose.

The process of monitoring for possible side effects of the vitamin regimen is outlined in Table 2. 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 end point is reached or the study is completed, which is projected for 1998.

Endpoints

The primary endpoints are diagnoses of lung cancer. The secondary endpoints are other malignant neoplasms and deaths from lung cancer, other cancers, cardiovascular disease, and all other causes. A well-defined process for evaluating endpoints has been implemented. Each presumed primary endpoint is reviewed by the pathologist for the coordinating center. The pathologist's assessment and other pertinent data are then independently reviewed by two physician members of the CARET endpoints committee. In cases of disagreement, the endpoints committee chair decides or brings the case for discussion in the committee, according to specific criteria. The review classifies the basis for the confirmation of cancer and the contribution of cancer to the death of the participant.

The primary analysis is for the incidence of lung cancer in the two high-risk populations, comparing treatment arm against placebo arm. Secondary analyses 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 as well as summaries of 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,

TABLE 3.—*Study Center Recruitment Goals and Progress*

Study Center	Goals			Randomized as of 3/31/92
	Asbestos	Smoking	Total	
Baltimore, Md	800	0	800	805
New Haven, Conn	1,000	0	1,000	821
Portland, Ore	660	4,000	4,660	3,180
San Francisco, Calif	800	0	800	699
Seattle, Wash				
Vanguard	816	1,029	1,845	1,845
Efficacy	201	4,300	4,501	3,204
Irvine, Calif (started late 1991)	0	4,300	4,300	155
Total	4,277	13,629	17,906	10,709

potential efficacy against coronary heart disease and other causes of death, roles of smoking in fibrosis and of fibrosis as an independent risk factor in lung cancer among the asbestos-exposed cohort, variation in β-carotene response among participants on similar dosages, smoking cessation success, and behavioral aspects of participation and compliance.

Common Questions From Physicians

Why do you use two agents? How will you be able to tell which is effective, if there is a favorable result? β-Carotene and vitamin A exert entirely different and quite complementary actions, which may be protective against specific aspects of the late stages of the carcinogenic process. We want to increase our possibility of success; this is more important than differentiating the roles of the two agents, especially since the portfolio of chemoprevention trials supported by the National Cancer Program also includes β-carotene alone (Harvard Physicians Study) and β-carotene plus vitamin E (two antioxidants, Finland trial).

What should I do if a patient of mine, participating in your trial, develops symptoms consistent with vitamin A toxicity? The symptoms of vitamin A toxicity, especially at the moderate dosage used in CARET, are nonspecific and relatively common. We have found no differences to date between the placebo and the treatment arms for any of the symptoms or signs or for liver function assays. Therefore, it is unlikely that headaches, change in bowel function, anxiety, depression, and the other monitored symptoms that do occur are due to the regimen administered in CARET. Sometimes specific causes can be ascertained, ranging from personal losses leading to depression to intercurrent infections causing local or systemic symptoms. We have a careful symptom management protocol, however (Table 2).

Does the treatment increase serum triglyceride or cholesterol levels? Should patients with moderate or high levels be excluded from CARET? We found no progressive increase in serum triglyceride levels and no exaggerated response in participants with initial elevated values. Serum cholesterol levels decrease slightly. Thus, we do not exclude subjects from CARET or stop the dosage based on the triglyceride or cholesterol values.

If the treatment is so benign, why not have patients just take β-carotene or even both agents on a prophylactic basis? The US Food and Drug Administration and National Cancer Institute have recently stated that use of these agents to prevent cancer is still experimental and that studies like CARET are essential to ascertain efficacy and to demonstrate safety.

Is β-carotene desirable as an antioxidant to prevent progression of atherosclerosis? Investigators in the Harvard Physicians Study reported that a small subgroup of their subjects receiving β-carotene seemed to have a lower incidence of cardiovascular endpoints.[21] This is stimulating plans for new studies.[22] These investigators and others have warned that any conclusions are grossly premature. The CARET study will provide a good opportunity to test this hypothesis.

Might β-carotene and vitamin A help against other cancers besides lung cancer? It is possible. We are specifically evaluating mesotheliomas in the asbestos-exposed cohort and are checking against a possible increase in prostate cancer, based on some unconfirmed epidemiologic associations. Other cancers do not occur frequently enough to have useful statistical power even in 18,000 older adults, but all cancer cases and all deaths are being analyzed.

How can I assist? We are eager to have referrals for CARET of potentially eligible and interested men and women. Furthermore, we are dependent on the participants' physicians to understand enough about CARET to be supportive of the project and to reinforce our efforts to keep our participants on the annual schedule for visits and on the dosage regimens. We welcome inquiries and referrals to the study centers (Table 4).

Conclusion

Several lines of research suggest that retinol, β-carotene, or both, may be effective and safe chemopreventive agents for lung cancer. Currently, two large studies are testing this

TABLE 4.—*β-Carotene and Retinol Efficacy Trials (CARET) Study Centers and Management*

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hypothesis and one is examining its preventive effect for all cancers.

The CARET study reported here evolved from successful pilot programs. It is unique in that its participant group consists of both smokers and asbestos-exposed workers and also that its regimen is a combination of β-carotene and vitamin A. It includes women as well as men.

Experience with prevention trials has shown some important differences in design and conduct from treatment studies. These differences include the problems of recruiting 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. In addition, there are management problems because of the scale of the operation. Participants in prevention trials are partners in research; they are not patients.

We expect CARET, combined with the results of the other two major trials, to determine by the end of the decade whether or not vitamin A and β-carotene can be recommended to occupationally defined high-risk groups and to the public as chemopreventive agents against lung cancer.

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Sarcoidosis Presenting With an Unusual Erythematous Rash and Persistent Hypercalcemia

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SARCOIDOSIS HAS been defined as a multisystem granulomatous disorder of unknown etiology that most commonly affects young adults and most frequently manifests initially with bilateral hilar lymphadenopathy, pulmonary infiltration, and skin or eye lesions.[1]

I describe the case of a patient who had an unusual erythematous annular rash and persistent hypercalcemia as the first signs of the disease. This case illustrates the wide variety of clinical manifestations of this fascinating disease.

Report of a Case

The patient was a previously healthy 61-year-old man who five months before admission had acute iritis, which was treated with topical corticosteroids. Subsequently, intermittent low-grade fevers, drenching night sweats, fatigue, loss of appetite, and an 11-kg (25-lb) weight loss developed.

Three months before admission, laboratory evaluation by another physician yielded the following results: serum calcium 3.12 mmol per liter (12.5 mg per dl), albumin 32 grams per liter (3.2 grams per dl), urea nitrogen 12.85 mmol per liter (36 mg per dl), creatinine 159 μmol per liter (1.8 mg per dl), and a nonreactive rapid plasma reagin test. The erythrocyte sedimentation rate and results of thyroid function tests were within normal limits. The chest roentgenogram showed a small calcified granuloma in the left mid-lung and minimal change from a film obtained 12 years before. Results of renal function studies and serum calcium measurements were within normal limits three years earlier.

Six weeks before admission, a nonpruritic erythematous rash developed on the patient's back and spread to the chest and extremities. Ultrasound studies revealed hepatosplenomegaly, cholelithiasis, and a small right kidney. Laboratory results were as follows: serum calcium 2.82 mmol per liter (11.3 mg per dl), albumin 27 grams per liter (2.7 grams per dl), urea nitrogen 11.42 mmol per liter (32 mg per dl), and creatinine 184 μmol per liter (2.2 mg per dl). Flexible sigmoidoscopy, barium enema, esophagogastroduodenoscopy, and bone scan showed no evidence of malignancy. Tests for carcinoembryonic antigen, prostate-specific antigen, and serum protein electrophoresis revealed no abnormalities.

The patient had a history of hypertension that was well controlled with the use of atenolol, abdominal aortic aneurysm repair five years previously, and persistent edema of both wrists and hands for five years. He had a 70-pack-year history of cigarette smoking.

On admission to hospital the patient appeared chronically ill and cachectic. Physical examination revealed extensive skin lesions and bilateral nonpitting edema of the hands. No ophthalmologic abnormalities were detected. Many annular,

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