The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study: Design, Methods, Participant Characteristics, and Compliance

THE ATBC CANCER PREVENTION STUDY GROUP

ABSTRACT *The Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study was a randomized, double-blind, placebo-controlled, 2 × 2 factorial design, primary prevention trial testing the hypothesis that alpha-tocopherol (50 mg/day) and beta-carotene (20 mg/day) supplements reduce the incidence of lung cancer and possibly other cancers. Total and disease-specific mortality and incidence of various diseases and symptoms were monitored for safety. Between 1985 and 1993, 29,133 eligible male smokers aged 50 to 69 years at entry were randomized to receive daily active supplements or placebo capsules for 5 to 8 years (median 6.1 years), accumulating 169,751 follow-up years. This report describes the study design, methods, and protocol as well as the baseline characteristics and capsule compliance of the participants. The ATBC Study is the largest lung cancer chemoprevention trial conducted to date. Ann Epidemiol 1994;4:1-10.*

KEY WORDS: Lung cancer, cancer, nutrition, trials, prevention, beta-carotene, alpha-tocopherol, compliance

INTRODUCTION

High dietary intakes of fruits and vegetables are consistently associated with lower risk of cancer in man (1, 2). In 1981, Peto and associates (3) proposed the protective factor to be beta-carotene (BC), a precursor of vitamin A with strong antioxidant properties. Alpha-tocopherol ([AT] vitamin E), another major lipid-soluble antioxidant present in the diet, has also been associated with cancer protection in epidemiological studies, although the relationship has generally been weaker than that for BC (4, 5). Evidence of a cancer-inhibiting role for both antioxidants has also been obtained from in vitro and animal experiments (6, 7).

Final proof for a protective role of an antioxidant in the prevention of human cancer can be obtained only from a sufficiently large controlled trial. The Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study was a randomized, double-blind, placebo-controlled, chemoprevention trial testing the hypothesis that increased intakes of AT and/or BC prevent lung cancer and possibly other cancers. The present report describes the rationale, design and implementation, baseline characteristics, and compliance of the ATBC Lung Cancer Prevention Study, which was conducted between 1985 and 1993 in southwestern Finland as a joint project between the National Public Health Institute of Finland and the U.S. National Cancer Institute.

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OBJECTIVES

The primary objective of this chemoprevention trial was to evaluate the effects of AT and BC on lung cancer incidence. Secondary objectives were to evaluate the effects of AT and BC on the incidence of other major cancers and, for safety reasons, to study overall and cause-specific mortality and incidence of other diseases.

STUDY DESIGN

Participants in the ATBC Lung Cancer Prevention Study were recruited from the total population of 14 adjoining areas of southwestern Finland (Figure 1). The participants were randomly assigned to one of four treatment groups: AT alone, AT and BC, BC alone, or placebo in a complete 2 × 2 factorial design. This design allowed cost-effective investigation of the efficacy and safety of the two agents in a single-trial setting (8). Because 50% of the participants received AT or BC and 50% did not, the effect of each agent can be analyzed separately, providing there is no interaction between them.

Randomization was performed in blocks of eight within each of the study areas. The daily dose of AT was 50 mg and BC was 20 mg. The dose of AT is five times the recommended dietary allowance (RDA) of the U.S. National Research Council (9). There is no recommendation for the

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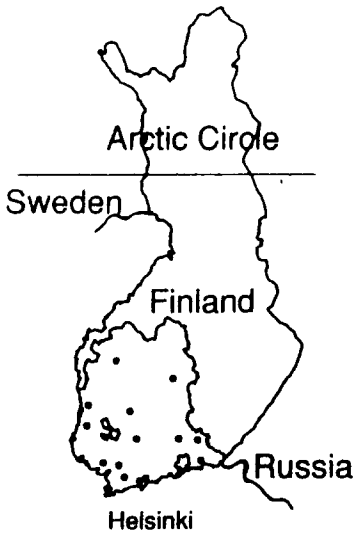

FIGURE 1. Outline of the ATBC Cancer Prevention Study region. The field centers are marked.

intake of BC; however, the RDA for vitamin A (1000 retinol equivalents) is equivalent to 6 mg of BC. Thus the dosage of BC is approximately three times the RDA of vitamin A. Synthetic AT was formulated as *dl*-alpha-tocopherol acetate (50% powder) and synthetic beta-carotene as 10% water soluble beadlets; all formulations were colored with quinoline yellow.

PILOT STUDY

A pilot study to determine the feasibility of a large-scale cancer chemoprevention trial was successfully conducted in one area with 236 participants in 1984–1985 (10).

ELIGIBILITY CRITERIA, RECRUITMENT AND EXCLUSIONS

To be eligible, the trial participants had to be male, between 50 and 69 years old, smoking five or more cigarettes per day at study entry, residing within the study region (Figure 1), and willing to participate with written, informed consent. Potential participants were excluded from the study for the following reasons: proven malignancy other than nonmelanoma skin cancer or carcinoma in situ; severe angina on exertion (Rose criteria, Grade 2) (11); chronic renal insufficiency; cirrhosis of liver; chronic alcoholism; receiving anticoagulant therapy; other medical problems that might limit participation for 6 years, such as psychiatric disorder or physical disability; current use of supplements containing vitamin E (>20 mg/d) or vitamin A (>20.000 IU/d = 4000 retinol equivalents) or BC (>6 mg/d).

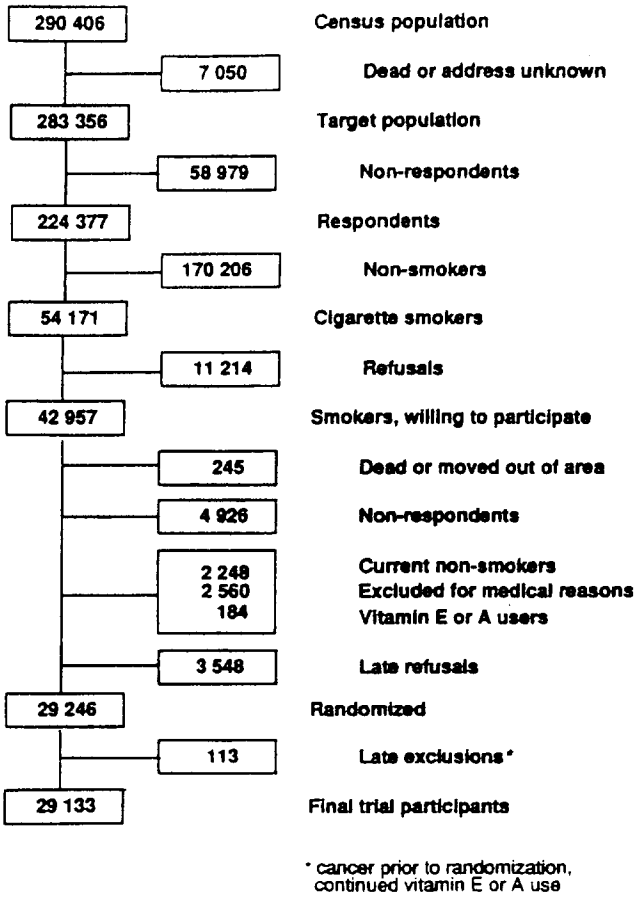

FIGURE 2. Recruitment of participants in the ATBC Study.

Figure 2 shows the number of men involved during the different phases of the recruitment process, including response, eligibility, exclusions, and randomization. The addresses of 283,356 of the 290,406 men aged 50 to 69 years residing in the study region were obtained from the Central Population Register. These men were mailed a questionnaire on their smoking habits and willingness to participate. Smokers of at least five cigarettes per day who expressed willingness to participate were then mailed an invitation to their local field center for further evaluation of their eligibility.

During the two clinic visits prior to randomization several procedures were performed and essential criteria checked. All procedures were conducted by specially trained, registered nurses. At the first baseline visit the men completed questionnaires on general background characteristics, medical, smoking, and occupational histories and on frequency of food use (12). Height, weight, blood pressure, heart rate, and visual acuity were measured. Serum samples were collected and stored deep frozen at −70°C for future analyses. The men were informed about the trial and signed consent forms. They were given a separate, detailed dietary history questionnaire (13) for completion at home. Finally,

the men were scheduled for a chest x-ray (CXR) to exclude existing lung cancer.

At their second baseline visit 2 weeks later, the dietary history questionnaire was returned and reviewed, and the men provided a toenail sample collected between visits. The CXR and final study eligibility were assessed, and the participant was then randomized into the trial. All the men received counseling from the nurses on the harmful effects of cigarette smoking.

Some men had reduced or stopped smoking cigarettes, or had changed to cigars or pipes since the mail survey or were not smokers at all (n = 2248). Medical reasons for exclusion were prior cancer (n = 716), effort angina (n = 440), anticoagulant treatment (n = 317), alcoholism and/or cirrhosis (n = 281), renal failure (n = 81), and miscellaneous conditions (mainly vitamin use, but also physical and mental handicaps) (n = 725).

A total of 29,246 men were randomized, of whom 113 were subsequently found to be ineligible and thus excluded, leaving 29,133 participants for the follow up. Reasons for late exclusions included postrandomization discovery, via the Finnish Cancer Registry, of a preexisting malignancy (n = 64), presence of undiagnosed lung cancer (n = 33) at baseline (i.e., a pulmonary lesion evident in the baseline CXR but not diagnosed as such until after randomization), continued spontaneous use of vitamin supplement (AT, BC, or vitamin A; n = 15), and nonsmoker status (n = 1). Most prestudy malignancies resulting in late exclusion were lip cancers reported by the participants as nonmelanoma skin cancers. The late exclusions were evenly distributed across the randomized groups.

Full-scale recruitment began in April 1985 and continued until the final sample size of over 29,000 men was achieved in June, 1988. Active intervention continued for all participants through April 30, 1993 and ranged from 5 to 8 years (median 6.1 years).

PARTICIPANT CHARACTERISTICS AT BASELINE

The catchment region for the study (Figure 1) included one-fourth of the total land area of Finland, but two-thirds of the population. Randomization strata varied in size from 456 to 8499 participants and included both urban and rural dwellers.

The median age of participants at the start of intervention was 57 years (Table 1). The median number of cigarettes smoked per day was 20, and the median duration of smoking was 36 years. Eighteen percent of subjects had had prior employment in an occupation reported to be associated with increased risk of lung cancer (including insulation work, mining, quarrying and foundry work, but excluding construction work in this study). The level of education for 79% of the participants was elementary school only, and nearly two-thirds lived in rural areas or towns of under 50,000 inhabitants. The median serum AT and BC concentrations were 11.5 mg/L and 171 μg/L, respectively. The median reported dietary intake of AT was 10.3 mg/day and BC 1.7 mg/day (Table 2).

The four randomized groups were of equal size (AT = 7286; AT and BC = 7278; BC = 7282; and placebo = 7287). There were no essential differences among the randomized groups in the medians or distributions of any of the characteristics examined. The few missing values were evenly distributed among the randomized groups. Moreover, drug interactions in man are generally rare and, in particular, no interaction of AT and BC was expected. For these reasons, treated and nontreated participants are compared in most data analyses and presentations (Tables 1 and 2). The AT-treated group was similar to the non-AT-treated group, and the BC group was similar to the non-BC group in all relevant aspects.

FOLLOW-UP EXAMINATION AND REVIEW

Follow-up consisted of three visits annually to the local field center, during which the men were asked about their health (illness and symptoms), use of nontrial vitamin supplements, and smoking habits since the last visit. Once a year, additional questions concerning cardiovascular and respiratory symptoms were asked, and measurements were made of blood pressure, heart rate, visual acuity, and weight.

A CXR was taken at 2.3 and 4.6 years and at the end of the study. At 3 years, the food frequency questionnaire and blood sampling were repeated for all participants. Close to the end of the intervention a whole-blood sample was again obtained. From the 2nd year of the trial onward, serum was also taken annually from a random sample of 700 to 800 participants.

CAPSULE DELIVERY AND COMPLIANCE

The study agents were provided in size 1, hard gelatin capsules dispensed in a wallet-style, calendar blister pack with a 4-month supply. During follow-up visits the capsule pack from the previous period was returned, residual capsules counted and recorded, and a new individual pack dispensed. A coded reserve supply of capsule packs was maintained centrally in the event of lost capsules requiring replacement. Careful monitoring of the capsule contents by the manufacturer and the research group guaranteed correct allocation and dose to the participants.

Compliance was determined from the number of supplied and returned capsules and was calculated by dividing the total number of unreturned capsules by the sum of

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TABLE 1. Baseline characteristics of subjects according to AT and BC treatment group assignment in the ATBC Study.

	Treatment			
	AT	No AT	BC	No BC
Number of subjects	14564	14569	14560	14573
Age				
Median	57.2	57.1	57.3	57.0
20%	52.7	52.7	52.8	52.6
80%	62.5	62.5	62.5	62.4
Cigarettes/day				
Median	20	20	20	20
20%	13	14	13	15
80%	25	25	25	25
Years smoked				
Median	36	36	37	36
20%	30	30	30	30
80%	43	43	43	43
Serum AT (mg/L)				
Median	11.5	11.5	11.5	11.4
20%	9.3	9.3	9.4	9.3
80%	14.2	14.1	14.2	14.1
Serum BC (μg/L)				
Median	171	171	171	170
20%	98	98	98	99
80%	289	291	291	290
Serum cholesterol (mmol/L)				
Median	6.2	6.2	6.2	6.2
20%	5.3	5.3	5.3	5.3
80%	7.2	7.1	7.2	7.1
Body mass index (w/h^2; kg/m^2)				
Median	26.0	25.9	26.0	26.0
20%	23.2	23.1	23.1	23.1
80%	29.2	29.2	29.2	29.2

days between visits. Capsules were available for counting in 99.7% of the active treatment time. Some 88% of participants took over 90% of their prescribed capsules on average during their active participation in the trial and only 4% were poor compliers (i.e., took less than 50% of capsules) (Figure 3). The estimated overall capsule consumption was 93% with no differences between treatment groups (93.4%, 93.2%, 93.2%, and 93.1% in the four randomized groups, respectively). Practically all poor compliers dropped out of the study during their 1st trial year.

LABORATORY MEASURES

Blood samples were collected from all participants who had been fasting 12 hours at the time of their first baseline visit. Samples were divided into 10 aliquots of 1.5 mL serum and stored at −70°C. Similar blood sampling and storage were repeated after 3 years of intervention.

The sera from baseline, 3-year, and annual random sampling were analyzed for AT, BC, retinol, total and HDL cholesterol. Determinations of AT, BC, and retinol were performed by high-performance liquid chromatography assay (14).

Serum concentrations of AT and BC were similar in the treatment groups at baseline, whereas during the intervention they were significantly higher in participants receiving active agent capsules compared to those not receiving that agent. After 3 years of intervention, serum levels of AT had increased by 50% in the treated individuals, whereas serum beta-carotene levels had increased 17-fold compared to baseline values. Based on random blood sampling, these AT and BC levels were maintained throughout the trial (Figure 4).

CHANGES IN RISK FACTORS DURING THE TRIAL

The number of cigarettes smoked daily remained similar across the treatment groups throughout the trial. Twenty-one percent of all participants stopped smoking (defined as two consecutive clinic visits during which they reported not smoking), and there was no difference across the treatment groups. Dietary intakes of AT, BC, and vitamin A remained practically unchanged throughout the intervention period.

DEATHS AND DROPOUTS

At the end of intervention, 20,072 participants were still active in the trial, and 25,563 were alive. Of the 9,061 not participating at the end, 3,570 had died and 5,491 were alive. Approximately half of those who died had dropped out of the study earlier for other reasons. The overall dropout rate during the 1st year was 11%, declining to 6% in the 2nd, and leveling off during the 3rd to 7th years at 4%. Death and illness were the two most common causes of dropping out (22% and 21%, respectively) followed by no contact (20%), and self-perceived side-effects (14%). The causes varied as the trial progressed. The most common reason during the 1st year was subjective side effects. Fewer subjects dropped out for this reason later on, whereas death and illness increased as a cause. The dropout rate varied only slightly across the four randomized groups (from 30.1% to 31.3%).

ENDPOINT ASCERTAINMENT

Endpoints occurring through April 30, 1993 are included as study events. Identification of incident cancers was primarily via the Finnish Cancer Registry, which provides almost 100% case ascertainment nationwide (15, 16). Participants were also asked to contact their field center if diagnosed with cancer. This hastened the identification of cancer cases, primarily among the active participants. Detection

TABLE 2. Baseline daily dietary intakes according to AT and BC treatment group assignment in the ATBC Study.

	Treatment			
	AT	No AT	BC	No BC
Number of subjects	13536	13575	13521	13590
Total energy (kcal)				
Median	2724.7	2714.7	2716.9	2722.3
20%	2157.9	2152.3	2160.3	2151.2
80%	3409.9	3410.5	3418.1	3404.2
Total fat (g)				
Median	117.7	116.9	117.4	117.2
20%	88.8	88.9	88.9	88.8
80%	153.5	153.4	153.5	153.3
Cholesterol (mg)				
Median	542.2	538.0	541.9	538.5
20%	389.7	388.8	389.1	389.7
80%	746.5	750.9	751.5	745.5
Alcohol (g)				
Median	11.1	10.9	10.9	11.1
20%	1.6	1.6	1.5	1.7
80%	29.6	29.4	29.5	29.5
Retinol (mg)				
Median	1.7	1.7	1.7	1.7
20%	1.0	1.0	1.0	1.0
80%	3.2	3.2	3.2	3.1
AT (mg)				
Median	10.3	10.3	10.3	10.2
20%	7.3	7.3	7.3	7.3
80%	15.1	15.4	15.4	15.2
BC (mg)				
Median	1.7	1.7	1.7	1.7
20%	0.9	0.9	0.9	0.9
80%	3.0	3.0	3.0	3.0
Vitamin C (mg)				
Median	97.0	97.4	97.5	96.9
20%	65.2	64.5	64.9	64.8
80%	140.2	140.8	141.0	140.1

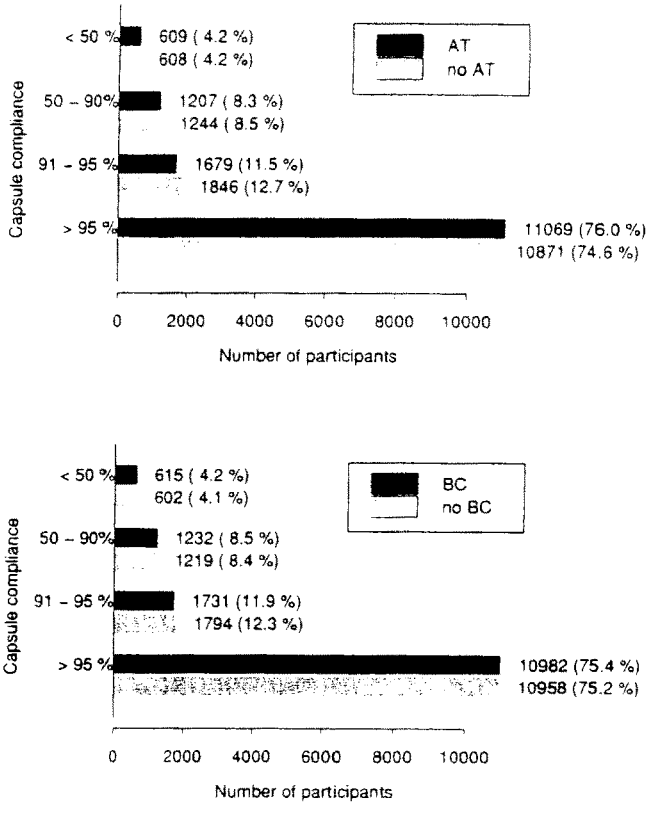

FIGURE 3. Capsule compliance among the active participants according to treatment during the ATBC Study.

of lung cancer was also enhanced by the two CXR screenings during follow-up visits and one at the end of the study. Special efforts were also made to obtain a CXR from the surviving dropouts at study termination, and this effort was highly successful. In all, 25,065 men had a terminal CXR, or 98% of those living at the time of invitation.

Once a possible cancer case was identified, all relevant medical records were collected, including results of diagnostic tests and procedures (imaging, endoscopy, cytology, biopsy, surgery, and pathology). These records and materials were gathered from the local hospitals, laboratories, and institutions by the ATBC Study personnel and examined at the study coordinating center.

Medical records for each case with a major cancer site (i.e., lung, prostate, colon, rectum, bladder, stomach, kidney, pancreas, larynx, liver, and unknown origin) were reviewed independently by two physicians participating in the study. If disagreement existed on the cancer diagnosis then a third physician reviewed the case and assigned a final diagnosis. For quality control purposes a random sample of these primary reviews was independently assessed by outside experts in oncology (see Appendix). Other cancer records were reviewed by one study physician. Pathology and cytology specimens were examined by one of the organ system-specific pathology review groups (Appendix), which assigned the final histopathologic diagnosis (WHO classification).

Deaths were verified via the Central Population Register, and death certificates were checked for the underlying cause of death. The noncancer diagnoses were ascertained through the National Hospital Discharge Register.

SAMPLE SIZE

Sample size calculations were based on the argument that a 25% reduction in lung cancer incidence in either AT or BC supplement users would constitute an effect of public health importance. Only one arm of the intervention was considered, and it was assumed that there was no interaction between AT and BC supplementation. Deaths and other dropouts and an assumed 1-year lag to maximum

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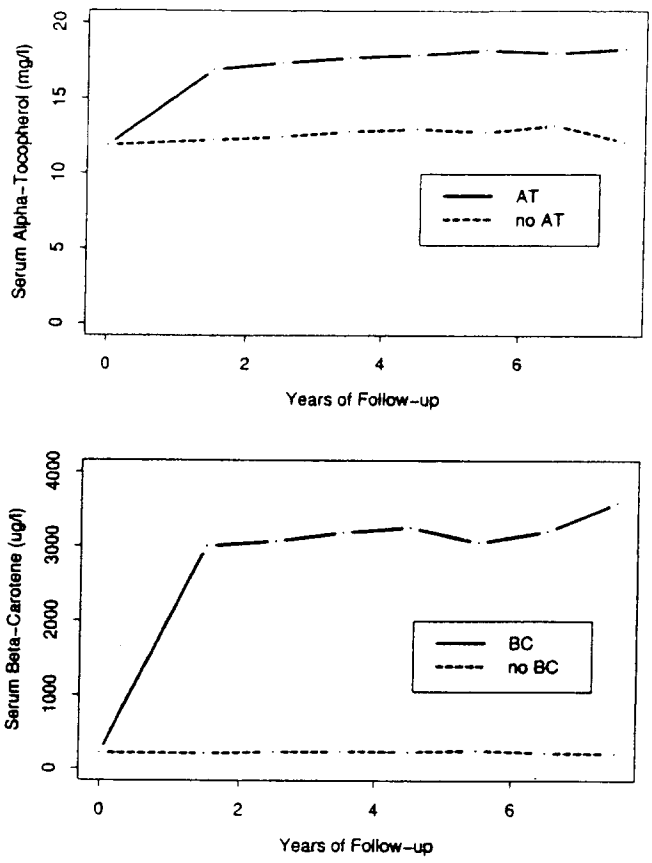

FIGURE 4. Serum AT and BC according to treatment in the ATBC Study.

efficacy diluted the 25% reduction requirement to an estimated 18.7%. Thus a total of 840 lung cancer cases needed to be observed in the trial cohort to obtain a study power of 85% (5% significance; two-sided test).

The required size of the trial cohort was initially estimated to be 18,000 for an intervention averaging 5 years. Calculations were based on age-specific lung cancer incidence rates for males published by the Finnish Cancer Registry and on age- and sex-specific mortality data for competing causes published by Statistics Finland. Rates were adjusted for smoking, assuming 30% of the general population smoked, a 10-fold risk of lung cancer among smokers, and a 1.7-fold increase in total mortality due to smoking.

During recruitment it became clear that the age distribution of study participants differed from that of the source population: those recruited were younger on average and thus the overall expected lung cancer incidence was lower than predicted. After 2 years of recruitment, the sample size assumptions were evaluated again. The required size of the trial cohort was reestimated at 27,000, with a mean intervention period of 6 years. Recruitment of the additional participants exceeded this goal, and 29,246 were randomized. Lung cancer cases observed during the intervention exceeded 800 and, thus, were well within predictions.

DATA MONITORING

A four-member Data and Safety Monitoring Committee (see Appendix) was convened twice annually to review study progress and scrutinize any side effects and unexpected toxicity.

Study Progress

General adherence to the study protocol was evaluated annually by monitoring recruitment success, rates of dropout and capsule compliance, timeliness and completeness of form handling and accuracy of the data base.

Safety

Potential side effects were monitored in several ways. A structured questionnaire covering 30 symptoms was filled in at each visit. In addition, all visits to doctors and hospitals were noted, and reasons for visits were recorded. Nurses and coordinating center physicians also made notes of any complaints and symptoms reported directly to them and these were coded into the database. Comparisons of some 300 items were done twice per year by trial treatment. The National Hospital Discharge Register was used to monitor diagnoses made in hospitals for the study participants.

Balance of Treatment Groups

Treatment group balance for risk factors, including smoking pattern, was evaluated twice per year. Other comparisons included cause-specific dropout rates, capsule compliance, and missing data.

Endpoints

After recruitment was completed, a comparison of endpoints according to the trial treatment was made annually according to the "intention to treat" principle. Standard survival analysis methodology was used, including plots of Kaplan–Meier survival curves and computation of log rank statistics. For lung cancer incidence, the follow-up time was recorded as the time to initial diagnosis of lung cancer, time to death, or time to the study closing date. For other cancers, a similar definition of follow-up time was used, ignoring other prior cancers. Cause-specific mortality data were analysed analogously.

DISCUSSION

The ATBC Cancer Prevention Study was designed and initiated to test the hypothesis that AT and BC, both agents

with strong antioxidant properties and low toxicity, protect against cancer. Early epidemiologic evidence on the inverse relation between lung cancer risk and dietary intake of BC and vitamin A (17–19) has since been confirmed in numerous follow-up and case-control studies that have related dietary intake or plasma concentration to cancer risk (20, 21). Furthermore, BC has also been shown to inhibit UV-induced skin cancers, oral carcinomas caused by dimethylbenzanthracene, and colon tumors induced by dimethylhydrazine treatment in laboratory animals (6). Various mechanisms have been proposed for the apparent protective effect of BC (22). These include provitamin-A activity, antioxidant properties, immunomodulation, and enzymatic activation of procarcinogens.

The 2 × 2 factorial design chosen for the trial allowed testing the effects of two, rather than just one, micronutrients in the same cohort for only a marginal increase in cost. The alternatives considered for the second agent included vitamin E, vitamin C, and selenium. Alpha-tocopherol was chosen because there were some data supporting its anticarcinogenic properties and no evidence of serious toxicity. Selenium-containing compounds were excluded because of insufficient information on their metabolism or safety in man. Evidence for cancer-protective effects of vitamin C was considered too preliminary to warrant testing in such an extensive intervention trial in humans (23).

Epidemiologic and experimental studies have since provided more evidence of the beneficial effects of AT (5). A majority of the case-control studies have shown lower concentrations of AT in the serum of patients with cancer than in controls. Cohort studies have generally shown a low level of serum AT to be associated with increased risk of cancer, although the strength of this association has varied among populations and subgroups and by cancer site. Alpha-tocopheral has been shown to inhibit the production of carcinogenic *N*-nitroso compounds from nitrites and amides, and it is one of the most important antioxidants in lipid membranes. Some studies have suggested that it inhibits the development of chemically induced tumors in experimental animals, such as those of soft tissue, mammary gland, skin, and large bowel (7).

A randomized, double-blind, placebo-controlled trial on the effects of AT and BC was considered timely as well as scientifically and ethically justified for several reasons. The suggestion that BC could reduce cancer incidence was one of the most promising of several untested hypotheses concerning inhibition of late-stage carcinogenesis by micronutrients. Alpha-tocopherol and BC were regarded as having essentially no side effects. Use of vitamin supplements was widespread and seemed likely to increase further, despite a lack of randomized evidence on side effects as well as health benefits. Conducting such trials as soon as possible appeared important, because such studies might have been logistically more difficult to perform later.

The choice of study population was based on scientific, practical, and ethical considerations. Smokers are at high risk of lung cancer and some other cancers (24); thus, the sample size needed to produce a definitive result was feasible. The balance between potential health benefit and unknown but possible toxicity was considered to be highly favorable, especially in subjects at high risk of lung cancer with their exceptionally poor prognosis. Men younger than 50 years were excluded because of their low cancer risk. On the other hand, although cancer is common above the age of 70, willingness to participate and adherence are lower and mortality is higher. In fact, the trial revealed early that interest in participation dropped sharply among men after 65 years, and their dropout rate was high.

Although the highly selected nature of this study population was scientifically well founded and logistically advantageous, there may be limits to the generalizability of the findings. Lack of an effect of AT or BC on smoking-related cancers in the age group studied will not exclude a beneficial effect of AT or BC in nonsmokers or in younger age groups. For example, the initiation of some cancers diagnosed in the trial may have occurred decades earlier. Moreover, the damaging effects of chronic cigarette smoking may prevent any protective activity of these agents. Whereas most lung cancer risk factors were assessed at baseline (for smoking, during follow-up also), exposure to radon, a known lung carcinogen, was not estimated because of the practical difficulty in documenting life-long residence histories and in obtaining valid measurements over the entire country.

The choice of smokers as the target group for a chemoprevention trial also raised ethical considerations in terms of both the study population and the general public. Effective prevention of smoking-associated cancers via nutritional supplements might provide an excuse for continuing to smoke despite the well-known harmful effects. To minimize this possibility, continuous antismoking counseling was provided by the nurses throughout the trial.

The doses of AT and BC were selected to maximize the preventive effect, while maintaining the integrity of the study and minimizing the possibility of any toxicity. For AT, the dose selected for the study (50 mg/day) represents an approximately fivefold excess over the mean dietary intake of the source population and exceeds the dietary intakes that have been associated with low cancer risks in epidemiologic studies. The dose for BC (20 mg/day) is 6 to 10 times that of the mean dietary intake in European and North American populations. This dose is also approximately threefold greater than the highest quintile of intake associated with the lowest risk of lung cancer in epidemiologic studies. A higher dose, as used in several subsequent trials (25–27), was rejected because participant safety was an overriding consideration in this study, which was one of the first large-scale chemoprevention trials to be launched. Furthermore, carotenodermia, commonly seen during high-

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dose carotenoid supplementation, would have partly unblinded the treatment regimen.

The study was terminated on schedule in early 1993 with a median duration of over 6 years. A longer trial was considered initially, but was rejected for economic reasons, and because it was thought that dropout and death rates would increase rapidly later in the study.

The assumption of a mere 1-year delay in the onset of reduction in incidence of lung cancer during the trial may have been overly optimistic in light of the 25- to 30-year interval between starting smoking and the rise in lung cancer risk. If one or both of the substances tested influences the early stages of carcinogenesis, the protective effects may become evident only after many more years. Fortunately, long-term follow up of the study cohort after ceasing active intervention is feasible because of the availability of nationwide disease registers and mortality statistics in Finland. Thus, relatively small late effects are detectable using extended register follow-up.

Although the ATBC Cancer Prevention Study was basically designed to test the hypothesis that AT and BC protect against lung cancer and possibly other cancers as well, it has also been possible to utilize data from various sources on other diseases. Although these data have been collected primarily for the purpose of safety monitoring, they may provide suggestive evidence for the effects of these vitamins on other diseases. Such information should only be used in support of results from other sources or in creating new hypotheses, as the effects of antioxidant vitamins on, for example, cardiovascular diseases did not feature in the original study hypothesis. The serum samples collected and stored at −70°C along with the extensive dietary data accumulated at baseline and during the follow-up will be used in observational studies, and these resources will become increasingly valuable during the coming years.

In conclusion, the ATBC Cancer Prevention Study has been a logistical success. Except for the lower than expected willingness of men between 65 and 70 years of age to participate, recruitment proceeded according to plan. The randomization also succeeded well: no differences were observed in relevant characteristics between the treatment groups at baseline. The changes in these characteristics during the trial were similar in the treatment groups with the obvious exception of serum AT and BC levels. Compliance was excellent, and the dropout rate was lower than expected. The total number of lung cancers observed during the study was in good agreement with the power calculations. The essentially complete case ascertainment has assured the comparability of trial treatment results.

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REFERENCES

1. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology, Cancer Causes Control. 1991;2:325–57.
2. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence, Nutr Cancer. 1992; 18:1–29.
3. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates?, Nature. 1981;290:201–8.
4. Menkes MS, Comstock GW, Vuilleumier JP, Helsing KJ, Rider AA, Brookmeyer R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer, N Engl J Med. 1986;315:1250–4.
5. Knekt P. Role of vitamin E in the prophylaxis of cancer, Ann Med. 1991;23:3–12.
6. Krinsky NI. Carotenoids and cancer in animal models, J Nutr. 1989; 119:123–6.
7. Prasad KN, Edwards-Prasad J. Vitamin E and cancer prevention: Recent advances and future potentials, J Am Coll Nutr. 1992;11:487–500.
8. Byar DP, Piantadosi S. Factorial designs for randomized clinical trials, Cancer Treat Rep. 1985;69:1055–63.
9. National Research Council. Recommended Dietary Allowances. 10th ed. Washington D.C.: National Academy Press; 1989.
10. Albanes D, Virtamo J, Rautalahti M, et al. Pilot study: The US-Finland lung cancer prevention trial, J Nutr Growth Cancer. 1986; 3:207–14.
11. Rose GA, Blackburn H. Cardiovascular Survey Methods. Monograph series 56. Geneva: World Health Organization; 1968.
12. Pietinen P, Hartman AM, Haapa E, et al. Reproducibility and validity of dietary assessment instruments. II. A qualitative food frequency questionnaire, Am J Epidemiol. 1988;128:667–76.
13. Pietinen P, Hartman AM, Haapa E, et al. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet, Am J Epidemiol. 1988; 128:655–66.
14. Milne DB, Botnen J. Retinol, alpha-tocopherol, lycopene, and alpha- and beta-carotene simultaneously determined in plasma by isocratic liquid chromatography, Clin Chem. 1986;32:874–6.
15. Kyllönen LEJ, Teppo L, Lehtonen M. Completeness and accuracy of registration of colorectal cancer in Finland, Ann Chir Gynaec. 1987; 76:185–90.
16. Pukkala E. Use of record linkage in small-area studies. In: Elliott P, Cuzick J, English D, Stern R, eds. Geographical and Environmental Epidemiology: Methods for Small-Area Studies. Oxford: Oxford University Press; 1992:125–31.
17. Bjelke E. Dietary vitamin A and human lung cancer, Int J Cancer. 1975;15:561–5.
18. Shekelle RB, Lepper M, Liu S, et al. Dietary vitamin A and risk of cancer in the Western Electric Study, Lancet. 1981; 2:1185–90.
19. Kvåle G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk, Int J Cancer. 1983;31:397–405.
20. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the risk of cancer, J Nutr. 1989;119:116–22.
21. Byers T, Perry G. Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers, Annu Rev Nutr. 1992;12: 139–59.
22. Bendich A, Olson JA. Biological actions of carotenoids, FASEB J. 1989;3:1927–32.

23. Willett WC, MacMahon B. Diet and cancer—An overview, N Engl J Med. 1984;310:633–8 and 697–703.

24. Fielding JE. Smoking: Health effects and control, N Engl J Med. 1985; 313:491–8.

25. Hennekens CH, Eberlein K. A randomized trial of aspirin and β-carotene among U.S. physicians, Prev Med. 1985;14:165–8.

26. Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of betacarotene to prevent basal-cell and squamous-cell cancers of the skin, N Engl J Med. 1990;323:789–95.

27. Thornquist MD, Omenn GS, Goodman GE, et al. Statistical design and monitoring of the Carotene and Retinol Efficacy Trial (CARET), Controlled Clin Trials. 1993;14:308–24.

APPENDIX
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