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THE EFFECT OF VITAMIN E AND BETA CAROTENE ON THE INCIDENCE OF LUNG CANCER AND OTHER CANCERS IN MALE SMOKERS

THE ALPHA-TOCOPHEROL, BETA CAROTENE CANCER PREVENTION STUDY GROUP*

Abstract *Background.* Epidemiologic evidence indicates that diets high in carotenoid-rich fruits and vegetables, as well as high serum levels of vitamin E (alpha-tocopherol) and beta carotene, are associated with a reduced risk of lung cancer.

Methods. We performed a randomized, double-blind, placebo-controlled primary-prevention trial to determine whether daily supplementation with alpha-tocopherol, beta carotene, or both would reduce the incidence of lung cancer and other cancers. A total of 29,133 male smokers 50 to 69 years of age from southwestern Finland were randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo. Follow-up continued for five to eight years.

Results. Among the 876 new cases of lung cancer diagnosed during the trial, no reduction in incidence was observed among the men who received alpha-tocopherol (change in incidence as compared with those who did not, −2 percent; 95 percent confidence interval, −14 to 12 percent). Unexpectedly, we observed a higher incidence of lung cancer among the men who received beta carotene than among those who did not (change in incidence, 18 percent; 95 percent confidence interval, 3 to 36 percent). We found no evidence of an interaction between alpha-tocopherol and beta carotene with respect to the incidence of lung cancer. Fewer cases of prostate cancer were diagnosed among those who received alpha-tocopherol than among those who did not. Beta carotene had little or no effect on the incidence of cancer other than lung cancer. Alpha-tocopherol had no apparent effect on total mortality, although more deaths from hemorrhagic stroke were observed among the men who received this supplement than among those who did not. Total mortality was 8 percent higher (95 percent confidence interval, 1 to 16 percent) among the participants who received beta carotene than among those who did not, primarily because there were more deaths from lung cancer and ischemic heart disease.

Conclusions. We found no reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or beta carotene. In fact, this trial raises the possibility that these supplements may actually have harmful as well as beneficial effects. (N Engl J Med 1994;330:1029-35.)

PREVIOUS studies have suggested that higher intakes of vitamin E (alpha-tocopherol) and beta carotene may be associated with a reduced risk of lung cancer. In particular, epidemiologic studies have linked the intake of vegetables rich in beta carotene with a lower risk of cancer (especially lung cancer) and have suggested that certain micronutrients are inhibitors of cancer.[1,2] The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study was a randomized, double-blind, placebo-controlled primary-prevention trial undertaken to determine whether supplementation with alpha-tocopherol, beta carotene, or both would reduce the incidence of lung cancer in male smokers. A secondary outcome of interest was the incidence of other cancers. Lung cancer was deemed a particularly appropriate target for this trial because of its high incidence, its generally poor prognosis, and the existence of a well-defined high-risk population (i.e., smokers).[3] In this report we describe the initial overall results of the study, which was conducted in Finland as a joint project of the National Public Health Institute of Finland and the U.S. National Cancer Institute.

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*The participants in the study group are listed in the Appendix.

METHODS

Study Design

The rationale, design, and methods of the study, the characteristics of the participants, and the measures of compliance have been described in detail elsewhere.[4] Briefly, the participants (n = 29,133) were male smokers who were 50 through 69 years old at entry; they were recruited from the total male population of this age group in 14 geographic areas in southwestern Finland (n = 290,406). The participants were randomly assigned to one of four supplementation regimens: alpha-tocopherol alone (n = 7286), alpha-tocopherol and beta carotene (n = 7278), beta carotene alone (n = 7282), or placebo (n = 7287). Thus, a total of 14,564 men received alpha-tocopherol, and 14,560 received beta carotene. The daily dose of alpha-tocopherol was 50 mg and that of beta carotene, 20 mg. Follow-up continued for 5 to 8 years (median, 6.1), until death or April 30, 1993, with a total of 169,751 person-years contributed by

the surviving participants. This study was approved by the institutional review boards of the participating institutions, and all subjects provided informed consent before randomization.

Eligibility

Participants were recruited in 1985 through 1988 from the respondents to a postal survey (n = 224,377) who lived in the designated study region. To be eligible, they had to be smokers (five or more cigarettes per day at entry), 50 to 69 years old, and willing to give informed written consent. Potential participants with a history of cancer or serious disease limiting their ability to participate, those taking supplements of vitamin E, vitamin A, or beta carotene in excess of predefined doses, and those being treated with anticoagulant agents were excluded. Before their enrollment, the participants were interviewed at 1 of 14 local study centers to obtain details of their medical, dietary, smoking, and occupational histories and information about other risk factors for cancer. Each participant's dietary intake of alpha-tocopherol and beta carotene was estimated from the diet-history questionnaire[5]; levels of alpha-tocopherol and beta carotene were measured in serum samples by high-performance liquid chromatography.[6] Participants identified after randomization as ineligible (n = 113) were equally distributed among the four intervention groups; they included men with preexisting cancer other than nonmelanoma skin cancer (n = 64), men with lung cancer identified on the base-line chest film (n = 33), users of vitamin supplements in excess of the study limits (n = 15), and 1 nonsmoker.

Randomization and Blinding

The participants at each of the 14 study sites were randomly assigned to one of the four intervention groups. Treatment assignments were based on a two-by-two factorial design that permitted assessment of the effects of the two supplements independently. Thus, half the participants received alpha-tocopherol (n = 14,564) and half did not (n = 14,569). Similarly, half received beta carotene (n = 14,560) and half did not (n = 14,573). The proportion of participants who reported yellowing of the skin at any time during active follow-up was 34 percent in the two groups that received beta carotene, as compared with 7 percent in the groups given no beta carotene; persistent yellowing of the skin (during two thirds or more of the follow-up visits) was reported by 8.8 percent of the participants who received beta carotene, as compared with 0.3 percent of those who did not. Participants and all study staff involved in the ascertainment of end points and the assignment of final diagnoses remained blinded to the participants' treatment assignments throughout the trial.

Delivery of Supplements and Assessment of Compliance

The study agents were formulated as synthetic *dl*-alpha-tocopheryl acetate (50 percent powder) and synthetic beta carotene (10 percent water-soluble beadlets); all formulations were colored with quinoline yellow. Capsules were packaged in coded blister-pack wallets in calendar format provided by Hoffmann–LaRoche (Basel, Switzerland). All participants took a single capsule daily. The participants received a new supply of capsules at each of their thrice-yearly follow-up visits. Visits began in April 1985 for some participants and were concluded in April 1993 for all. Compliance was assessed by counts of the remaining capsules at each visit, by measurement of serum alpha-tocopherol and beta carotene levels after three years of supplementation, and by measurements in random serum samples throughout the study.[4]

Assessment of End Points

Cases of lung cancer were identified through the Finnish Cancer Registry.[7] All cases known to have been diagnosed up to April 30, 1993, are included in this report. To enhance the ascertainment of cases, a chest film was obtained at a study visit every 28 months and at each participant's exit from the study. For various reasons, the final chest film was not available for 494 of the surviving men. There were no differences among the intervention groups in the proportion of exit chest films available for analysis or in the reasons why no film was obtained. All diagnostic information for each case of lung cancer was reviewed by the Clinical Review Committee for confirmation and staging. Clinical diagnoses were based on histologic features in 77 percent of the cases, on cytologic analysis alone in 15 percent, and on clinical data alone in 8 percent.

Cancers other than lung cancer were also identified through the Finnish Cancer Registry, with medical records reviewed by clinicians at the central study office.

Monitoring of Safety and Efficacy

Possible side effects of the interventions were assessed at each follow-up visit by means of a questionnaire covering symptoms and an interview focusing on illnesses since the most recent visit that had led to a visit to a doctor or to hospitalization. Information on morbidity unrelated to cancer was also obtained from the Finnish National Hospital Discharge Registry. Deaths (n = 3570) were identified from the National Death Registry, a branch of Statistics Finland. The underlying cause of death was coded by trained nosologists using the *International Classification of Diseases*, ninth revision (ICD-9), and reviewed at the study coordinating center; the death certificate was not available for four participants. In 91 percent of all deaths, the cause was based on the autopsy findings (54 percent), the inpatient diagnosis, or both.

A data and safety monitoring committee was convened twice annually throughout the study to review its progress and integrity and to evaluate unblinded data relevant to safety and efficacy.

Statistical Analysis

Analyses of trial results focused on estimating the overall effect of the two supplements on the incidence of cancer and on mortality due to cancer or other causes. Analyses were based on the intention-to-treat principle; that is, follow-up and case ascertainment continued regardless of whether participants continued in the trial. We tested for an interaction between the effects of alpha-tocopherol and beta carotene by means of a proportional-hazards model.[8]

Kaplan–Meier cumulative-incidence plots and two-sided nominal P values derived from the unweighted log-rank statistic[8] are presented for each intervention separately: alpha-tocopherol as compared with no alpha-tocopherol, and beta carotene as compared with no beta carotene. The effect of intervention is expressed as the percentage change in the incidence of an end point and its 95 percent confidence interval. Computations of confidence intervals were based on the binomial distribution, derived from conditioning on the number of cases and adjustment of probabilities for the number of person-years of follow-up in the two comparison groups.[8,9]

The preliminary data on cancers other than lung cancer are presented in the form of counts and rates of incidence according to intervention group. Two or more of the five primary cancers in a single participant were counted as separate cases in each category, but were counted only once within each category (even in the category "other cancers"). Thus, the cancer counts are not mutually exclusive. Cases of carcinoma in situ of the lung (n = 6) and basal-cell carcinoma of the skin (n = 217) were excluded from the analysis. Cause-specific data on deaths are presented in the form of counts and mortality rates in mutually exclusive cause-of-death categories according to intervention group. The categories are based on the following ICD-9 codes: cancer (140 through 208), ischemic heart disease (410 through 414), hemorrhagic stroke (430 through 432), ischemic stroke (433 through 436 and 438), other cardiovascular disease (390 through 405, 415 through 429, 437, and 440 through 459), injuries and accidents (800 through 999), and other causes (001 through 139, 210 through 389, and 460 through 799). Only cases in which cancer was the underlying cause of death were included among the deaths due to cancer.

Results

Characteristics of the Participants

At study entry, the men in the cohort averaged 57.2 years of age, smoked an average of 20.4 cigarettes daily, and had smoked for an average of 35.9 years.

There were no differences among the intervention groups with respect to any characteristic or risk factor for lung cancer that we evaluated at base line (Table 1) or during follow-up, except those directly related to supplementation. A total of 6131 participants stopped smoking during the trial; the numbers who quit in the various intervention groups differed by less than 26. Similarly, 9061 participants left the study for any reason, including death; the groups differed in the number of such dropouts by less than 37.

Lung Cancer and Base-Line Alpha-Tocopherol and Beta Carotene Levels

When the placebo group was divided according to quartiles with regard to the base-line serum alpha-tocopherol or beta carotene concentration, the incidence of lung cancer was higher among the subjects in the lowest quartile group than among those in the highest (incidence per 10,000 person-years, lowest vs. highest quartile group: alpha-tocopherol, 56.8 vs. 41.8; beta carotene, 53.3 vs. 43.1). There was, moreover, an inverse association between dietary intake of alpha-tocopherol and beta carotene at base line and the risk of lung cancer during the trial (incidence per 10,000 person-years, lowest vs. highest: alpha-tocopherol, 61.4 vs. 40.6; beta carotene, 47.9 vs. 39.9).

Compliance

Compliance, estimated on the basis of residual-capsule counts, was excellent, with four out of five active participants taking more than 95 percent of their capsules. In addition, there were no differences in capsule consumption among the intervention groups (median percentage of capsules taken, 99.0 percent in each). Participants receiving active treatment accounted for 86 percent of the total follow-up, whereas the remaining 14 percent was contributed by men who died or dropped out and therefore did not consume capsules. Compliance with intervention was confirmed by the substantial increases in serum alpha-tocopherol and beta carotene concentrations in the groups receiving the active agents, whereas the levels changed little in those who did not receive the agents (Table 2).

Incidence of Lung Cancer and Mortality

A total of 876 newly diagnosed cases of lung cancer and 564 deaths due to lung cancer were identified in the entire cohort. There was no evidence of an interaction between the two supplements in their effect on lung cancer (incidence per 10,000 person-years: alpha-tocopherol alone, 47.3; alpha-tocopherol and beta carotene, 55.3; beta carotene alone, 57.2; and placebo, 47.7; likelihood-ratio test for interaction: chi-square = 0.04, P = 0.84). Our findings regarding the incidence of lung cancer and mortality from that disease according to intervention are shown in Figures 1, 2, and 3. For alpha-tocopherol recipients, the small reduction in incidence (2 percent) during the entire trial was not statistically significant (P = 0.8 by the log-rank test). Among the men who received beta carotene, an excess cumulative incidence of lung cancer was observed after 18 months and increased progressively thereafter, resulting in an 18 percent difference in incidence by the end of the study (95 percent confidence interval, 3 to 36 percent; P = 0.01) between the participants who received beta carotene and those who did not. The results were essentially identical when the analysis was restricted to men who had no yellowing of the skin or to those with lung cancers detected radiographically during the study. Mortality due to lung cancer was also apparently higher in the groups that received beta carotene than in those that did not (P = 0.08). No difference associated with the presence or absence of beta carotene supplementation was observed in the case fatality rate or in the length of time from diagnosis to death.

The six cases of carcinoma in situ that were excluded from these analyses were distributed as follows: three each among participants who received alpha-tocopherol and those who did not, and two cases among participants who received beta carotene and four among those who did not. There was one new

Table 1. Median Base-Line Characteristics of the Participants, According to Whether They Received Alpha-Tocopherol and Beta Carotene.*

Characteristic	Alpha-Tocopherol	No Alpha-Tocopherol	Beta Carotene	No Beta Carotene
No. of subjects	14,564	14,569	14,560	14,573
Age (yr)	57.2	57.1	57.3	57.0
Cigarettes smoked/day	20	20	20	20
Years of smoking	36	36	37	36
Serum cholesterol (mmol)	6.2	6.2	6.2	6.2
Body-mass index†	26.0	25.9	26.0	26.0
Total energy intake (kcal/day)	2,725	2,715	2,717	2,722
Total fat intake (g/day)	117.7	116.9	117.4	117.2
Alcohol intake (g/day)	11.1	10.9	10.9	11.1

*This was a two-by-two study, with a total of 29,133 participants. The numbers with data on the dietary-intake variables are as follows: alpha-tocopherol, 13,536; no alpha-tocopherol, 13,575; beta carotene 13,521; and no beta carotene, 13,590.

†The weight in kilograms divided by the square of the height in meters.

Table 2. Serum Concentrations of Alpha-Tocopherol and Beta Carotene before and after Supplementation, According to Intervention.*

Index and Group	No. of Subjects	Median	20th Percentile	80th Percentile
		milligrams per liter		
Alpha-tocopherol level				
At base line				
Alpha-tocopherol	14,472	11.5	9.3	14.2
No alpha-tocopherol	14,469	11.4	9.3	14.1
At three years				
Alpha-tocopherol	11,332	17.3	14.3	21.1
No alpha-tocopherol	11,258	12.4	10.2	15.1
Beta carotene level				
At base line				
Beta carotene	14,460	0.17	0.10	0.29
No beta carotene	14,460	0.17	0.10	0.29
At three years				
Beta carotene	11,276	3.0	1.6	4.5
No beta carotene	11,314	0.18	0.10	0.30

*To convert values for alpha-tocopherol to millimoles per liter, multiply by 2.322. To convert values for beta carotene to millimoles per liter, multiply by 1.863.

case of lung cancer among the 113 participants excluded after randomization; the man was assigned to receive alpha-tocopherol.

Other Cancers

A total of 1415 first cancers other than lung cancer were identified in 1331 subjects during the trial (basal-cell carcinoma of the skin was excluded, as were second cancers at a given site). Figure 2 shows the number of first cancers and their incidence, according to intervention group, at the five most common sites and at all other sites combined. The participants who received alpha-tocopherol had fewer cancers of the prostate and colorectum than those who did not receive alpha-tocopherol, whereas more cancers of the bladder, stomach, and other sites combined were diagnosed in the participants who received this supplement. The participants who received beta carotene had more cancers of the prostate and stomach and fewer cases of other cancers than those who did not receive beta carotene. There were two cancers other than lung cancer (melanoma and astrocytoma) among the participants who were excluded after randomization.

Mortality

Altogether, 3570 deaths occurred during the trial. Among participants receiving alpha-tocopherol, there were fewer deaths caused by ischemic heart disease and ischemic stroke than there were among those who did not receive alpha-tocopherol, but more deaths due to cancers other than lung cancer or due to hemorrhagic stroke (Fig. 3). Overall mortality was 2 percent higher in the alpha-tocopherol groups than in the groups that received no alpha-tocopherol (95 percent confidence interval, −5 to 9 percent; P = 0.6). There were more deaths due to lung cancer, ischemic heart disease, and ischemic and hemorrhagic stroke among recipients of beta carotene (Fig. 3). Overall mortality was 8 percent higher among the participants who received beta carotene than among those not given beta carotene (95 percent confidence interval, 1 to 16 percent; P = 0.02).

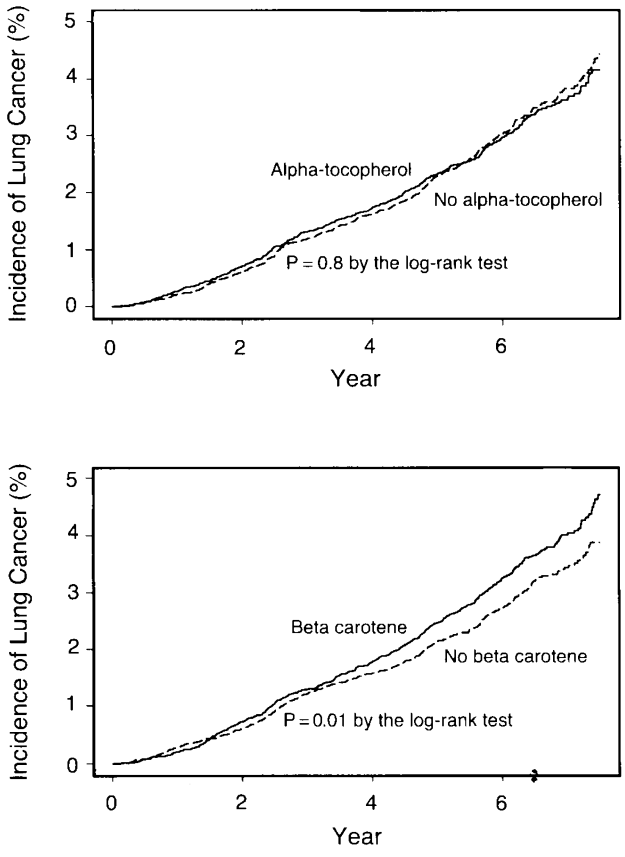

Figure 1. Kaplan–Meier Curves for the Cumulative Incidence of Lung Cancer among Participants Who Received Alpha-Tocopherol Supplements and Those Who Did Not (Upper Panel) and among Participants Who Received Beta Carotene Supplements and Those Who Did Not (Lower Panel).

Data are shown only through 7½ years of follow-up because of the small numbers of participants beyond that time.

Discussion

Our results provide no evidence of a beneficial effect of supplemental vitamin E (alpha-tocopherol) or beta carotene in terms of the prevention of lung cancer. In fact, men who received beta carotene were found to have lung cancer more frequently than those who did not receive beta carotene. These results are sufficiently strong that it is highly unlikely that 20 mg of beta carotene per day confers any material protective effect against lung cancer among smokers over a period of about six years.

The lack of reduction in the incidence of lung cancer among the men given supplemental beta carotene may be explained by bias, an inadequate duration of supplementation, the use of the wrong dose, or an inappropriate study population. Bias can be discounted, since the intervention groups were balanced in terms of all the relevant characteristics we studied. The study population was large, and case ascertainment was essentially complete. In addition, the men in the various intervention groups sought treatment at virtually the same time for lung cancer, as measured by the length of time from diagnosis to death, and even for such minor problems as yellowing of the skin. Moreover, analyses of the incidence of lung cancer that were restricted to participants who did not report yellowing of the skin or to cases diagnosed on the chest film obtained at the study examination yielded results similar to those for the entire cohort; this similarity of results essentially rules out bias caused by self-selection or by differences in diagnostic procedures.

It is plausible that the intervention period was too short to inhibit the development of cancers resulting from a lifetime of exposure to cigarette smoke and other carcinogens. Beta carotene may not be the active cancer-inhibiting component of the fruits and vegetables identified as protective in observational studies, or the intake of beta carotene may be only a nonspecific marker for lifestyles that protect against cancer.

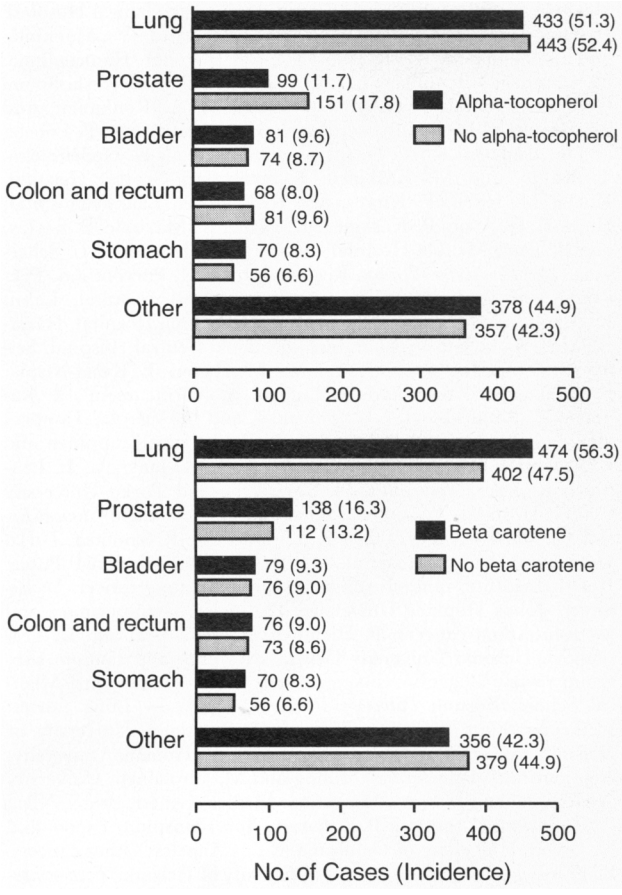

Figure 2. Number and Incidence (per 10,000 Person-Years) of Cancers, According to Site, among Participants Who Received Alpha-Tocopherol Supplements and Those Who Did Not (Upper Panel) and among Participants Who Received Beta Carotene Supplements and Those Who Did Not (Lower Panel).

Although it is conceivable that the dose we used was too low, this seems unlikely, since that dose exceeded by many times the dietary intake of beta carotene in epidemiologic studies that found a strong inverse association between the consumption of carotene-rich foods and the incidence of lung cancer.[10,11] Finally, study findings regarded as showing supplementation to be beneficial or harmful may occur by chance.

The lack of benefit of beta carotene is particularly surprising given the substantial and consistent epidemiologic evidence of an association between a higher beta carotene intake and a lower incidence of lung cancer,[11-15] including the results of the cohort-based analysis in this study. Furthermore, a recent large trial in China found a significant reduction in mortality due to cancer among persons whose diets were supplemented daily with the combination of beta carotene (15 mg), alpha-tocopherol (30 mg), and selenium (50 μg) for 5¼ years.[16]

We also observed no beneficial effect of alpha-tocopherol on the incidence of lung cancer or on mortality due to this disease. At the start of the trial, the a priori evidence that alpha-tocopherol prevented lung cancer was less substantial than that for beta carotene, and since then little additional evidence has been accumulated.[17-19] Possible explanations for the lack of effect are similar to those for beta carotene, although the relatively low dose and the short duration of supplementation merit greater consideration in the case of alpha-tocopherol. Furthermore, we observed no interaction between alpha-tocopherol and beta carotene in their effect on the incidence of lung cancer.

The apparently protective effect of alpha-tocopherol against prostate cancer and, to a lesser extent, against colorectal cancer is intriguing. Although there was little or no evidence linking alpha-tocopherol to the incidence of cancers at either of these sites when the trial started, limited observational data consistent with these findings have now been published.[20-22] Although these results are suggestive, many comparisons with these two agents were made in these analyses, increasing the possibility that some of the apparent benefits may have occurred by chance alone. Additional data from the continued follow-up

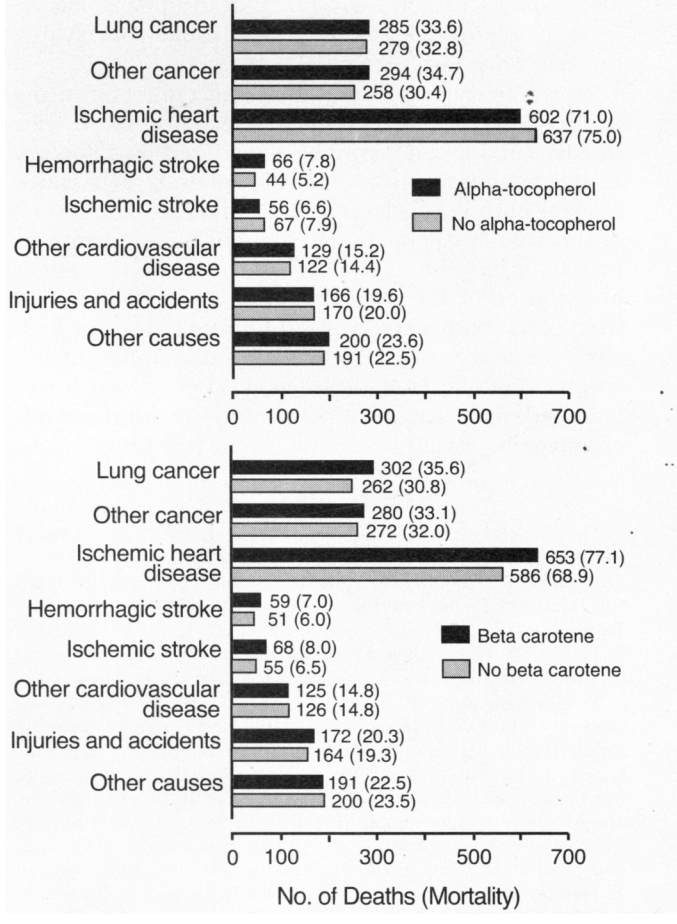

Figure 3. Deaths and Mortality Rates (per 10,000 Person-Years), According to Cause of Death, among Participants Who Received Alpha-Tocopherol Supplements and Those Who Did Not (Upper Panel) and among Participants Who Received Beta Carotene Supplements and Those Who Did Not (Lower Panel).
The cause of death was unknown for four participants.

of the participants in this and other intervention studies are needed before conclusions can be drawn about the role of alpha-tocopherol in preventing these cancers.

Our results raise the possibility that supplementation with beta carotene may be harmful in smokers. The higher mortality due to ischemic heart disease and lung cancer among the beta carotene recipients requires more detailed analysis, and information from other studies is also needed. We are aware of no other data at this time, however, that suggest harmful effects of beta carotene, whereas there are data indicating benefit.[16,23] Furthermore, there are no known or described mechanisms of toxic effects of beta carotene, no data from studies in animals suggesting beta carotene toxicity, and no evidence of serious toxic effects of this substance in humans.[24] In the light of all the data available, an adverse effect of beta carotene seems unlikely; in spite of its formal statistical significance, therefore, this finding may well be due to chance.

The higher mortality due to hemorrhagic stroke among the participants receiving alpha-tocopherol also requires careful review. Alpha-tocopherol has effects on platelet function[25,26] that could conceivably underlie this observation.

In summary, we found no overall reduction in the incidence of lung cancer or in mortality due to this disease among male smokers who received dietary supplementation with alpha-tocopherol, beta carotene, or both in this large trial in Finland. The results of this study raise the possibility that these substances may have harmful as well as beneficial effects. Longer observation of the participants in this trial and data from other studies of people at normal risk[27,28] or high risk[29] for cancer will be required to determine the full spectrum of effects of these agents. Public health recommendations about supplementation with these micronutrients would be premature at this time.

Appendix

The participants in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group were as follows: *Principal investigators* — O.P. Heinonen and J.K. Huttunen, National Public Health Institute, Helsinki, Finland, and D. Albanes, National Cancer Institute, Bethesda, Md.; *Senior investigators* — J. Haapakoski, J. Palmgren, P. Pietinen, J. Pikkarainen, M. Rautalahti, and J. Virtamo, National Public Health Institute, and B.K. Edwards, P. Greenwald, A.M. Hartman, and P.R. Taylor, National Cancer Institute; *Investigators* — J. Haukka, P. Järvinen, N. Malila, and S. Rapola, National Public Health Institute; *Data management* — P. Jokinen, A. Karjalainen, J. Lauronen, J. Mutikainen, M. Sarjakoski, A. Suorsa, M. Tiainen, and M. Verkasalo, National Public Health Institute, and M. Barrett, Information Management Services, Silver Spring, Md.; *Laboratory measurements* — G. Alfthan, C. Ehnholm, C.G. Gref, and J. Sundvall, National Public Health Institute; *Nutritionists* — E. Haapa, M.L. Ovaskainen, M. Palva-Alhola, and E. Roos, National Public Health Institute; *Cancer Registry* — E. Pukkala and L. Teppo, Finnish Cancer Registry, Helsinki; *Data and Safety Monitoring Committee* — H. Frick (chairman), University of Helsinki, Helsinki, A. Pasternack, University of Tampere, Tampere, Finland, B.W. Brown, Jr., Stanford University, Palo Alto, Calif., and D.L. DeMets, University of Wisconsin, Madison; *Collaborating hospitals in Finland* — Coordinators: K. Kokkola, National Public Health Institute, and E. Tala, Turku University Central Hospital, Paimio; Härmä Hospital, Alahärmä: E. Aalto, V. Mäenpää, and L. Tienhaara; Kanta-Häme Central Hospital, Hämeenlinna: M. Järvinen, I. Kuuliala, L. Linko, and E. Mikkola; Keski-Suomi Central Hospital, Jyväskylä: J. Nyrhinen, A. Ronkanen, and A. Vuorela; Kiljava Hospital, Nurmijärvi: S. Koskinen, P. Lohela, and T. Viljanen; Kotka Health Center Hospital: K. Godenhjelm, T. Kallio, and M. Kaskinen; Kymenlaakso Central Hospital, Kotka: M. Havu, P. Kirves, and K. Taubert; Laakso Hospital, Helsinki: H. Alkio, R. Koskinen, K. Laine, K. Mäkitalo, S. Rastas, and P. Tani; Meltola Hospital, Karjaa: M. Niemistö, T.L. Sellergren, and C. Äikäs; Porvoo Regional Hospital, Porvoo: P.S. Pekkanen and R. Tarvala; Päijät-Häme Central Hospital, Lahti: K. Alanko, K. Mäkipaja, and S. Vaara; Satalinna Hospital, Harjavalta: H. Siuko and V. Tuominen; Seinäjoki Central Hospital, Seinäjoki: L. Ala-Ketola, A. Haapanen, M. Haveri, L. Keski-Nisula, E. Kokko, M. Koskenkari, P. Linden, A. Nurmenniemi, R. Raninen, T. Raudaskoski, S.K. Toivakka, and H. Vierola; Tampere Health Center Hospital, Tampere: S. Kyrönpalo-Kauppinen and E. Schoultz; Tampere University Hospital: M. Jaakkola, E. Lehtinen, K. Rautaseppä, and M. Saarikoski; and Turku University Central Hospital, Turku: K. Liippo and K. Reunanen; *Clinical Review Committee* — Lung cancer: K. Liippo and E.R. Salomaa, Turku University Central Hospital, and J. Virtamo, National Public Health Institute; random subgroup review of lung cancer: D. Ettinger, Johns Hopkins University, Baltimore; Genitourinary and gastrointestinal cancers: P. Hietanen, H. Mäenpää, and L. Teerenhovi, Helsinki University Central Hospital; and random subgroup review of genitourinary cancers: G. Prout, Harvard Medical School, Boston; *Pathology Review Committee* — Lung cancer: L. Teppo, Finnish Cancer Registry, E. Taskinen, University of Helsinki, and F. Askin and Y. Erozan, Johns Hopkins University; Genitourinary cancers: S. Nordling and M. Virolainen, University of Helsinki, and L. Koss, Montefiore Medical Center, Bronx, N.Y.; Gastrointestinal cancers: P. Sipponen, Jorvi Hospital, Espoo, and K. Lewin, University of California at Los Angeles; Other cancers: K. Franssila and P. Kärkkäinen, University of Helsinki; *Food-composition research* — M. Heinonen, L. Hyvönen, P. Koivistoinen, V. Ollilainen, V. Piironen, and P. Varo, University of Helsinki; and *Capsule development and distribution* — W. Bilhuber, R. Salkeld, W. Schalch, and R. Speiser, Hoffmann–LaRoche, Basel, Switzerland.

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