

Controlled Trial of α -Tocopherol and β -Carotene Supplements on Stroke Incidence and Mortality in Male Smokers

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Abstract—Observational data suggest that diets rich in fruits and vegetables and with high serum levels of antioxidants are associated with decreased incidence and mortality of stroke. We studied the effects of α -tocopherol and β -carotene supplementation. The incidence and mortality of stroke were examined in 28 519 male cigarette smokers aged 50 to 69 years without history of stroke who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study). The daily supplementation was 50 mg α -tocopherol, 20 mg β -carotene, both, or placebo. The median follow-up was 6.0 years. A total of 1057 men suffered from incident stroke: 85 men had subarachnoid hemorrhage; 112, intracerebral hemorrhage; 807, cerebral infarction; and 53, unspecified stroke. Deaths due to stroke within 3 months numbered 38, 50, 65, and 7, respectively (total 160). α -Tocopherol supplementation increased the risk of subarachnoid hemorrhage 50% (95% CI -3% to 132% , $P=0.07$) but decreased that of cerebral infarction 14% (95% CI -25% to -1% , $P=0.03$), whereas β -carotene supplementation increased the risk of intracerebral hemorrhage 62% (95% CI 10% to 136% , $P=0.01$). α -Tocopherol supplementation also increased the risk of fatal subarachnoid hemorrhage 181% (95% CI 37% to 479% , $P=0.01$). The overall net effects of either supplementation on the incidence and mortality from total stroke were nonsignificant. α -Tocopherol supplementation increases the risk of fatal hemorrhagic strokes but prevents cerebral infarction. The effects may be due to the antiplatelet actions of α -tocopherol. β -Carotene supplementation increases the risk of intracerebral hemorrhage, but no obvious mechanism is available. (*Arterioscler Thromb Vasc Biol.* 2000;20:230-235.)

Key Words: α -tocopherol ■ β -carotene ■ cerebral infarction ■ intracerebral hemorrhage ■ subarachnoid hemorrhage

High amounts of fruits and vegetables in the diet^{1,2} as well as diets rich in antioxidant vitamins³ have been associated with decreased incidence of stroke. A similar inverse relation has been observed between serum concentrations of antioxidant vitamins and the risk of fatal stroke.^{4,5} These findings suggest that the antioxidants may be effective in the primary prevention of stroke. However, associations shown by observational studies, particularly weak ones, must not be causal, because the elimination of both known and especially unknown confounders is difficult, if not impossible. These limitations are abolished in large controlled trials, such as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study),^{6,7} in which evaluation of the effects of α -tocopherol and β -carotene on cardiovascular diseases was incorporated into the study protocol. In the present study, we report the effects of these antioxidant vitamins on the incidence and mortality from hemorrhagic and ischemic strokes among the participants of the ATBC Study.

Methods

The ATBC Study was a randomized, double-blind, placebo-controlled, 2×2 factorial design trial primarily testing the hypothesis that α -tocopherol and β -carotene supplements reduce the incidence of lung and other cancers. From 1985 to 1988, 29 246 male smokers (≥ 5 cigarettes per day) from the total male population aged 50 to 69 years of southwestern Finland ($n=290\ 406$) were recruited and randomized to 1 of 4 intervention regimens: α -tocopherol alone at 50 mg per day, β -carotene alone at 20 mg per day, α -tocopherol plus β -carotene, or placebo (Figure 1). Potential participants with a history of cancer or serious illness limiting long-term participation, those taking supplements of vitamin E, vitamin A, or β -carotene in excess of predefined doses, and those being treated with anticoagulants were excluded. All participants gave written informed consent, and the study was approved by the institutional review boards of the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Md.

Received April 1, 1999; revision accepted July 27, 1999.

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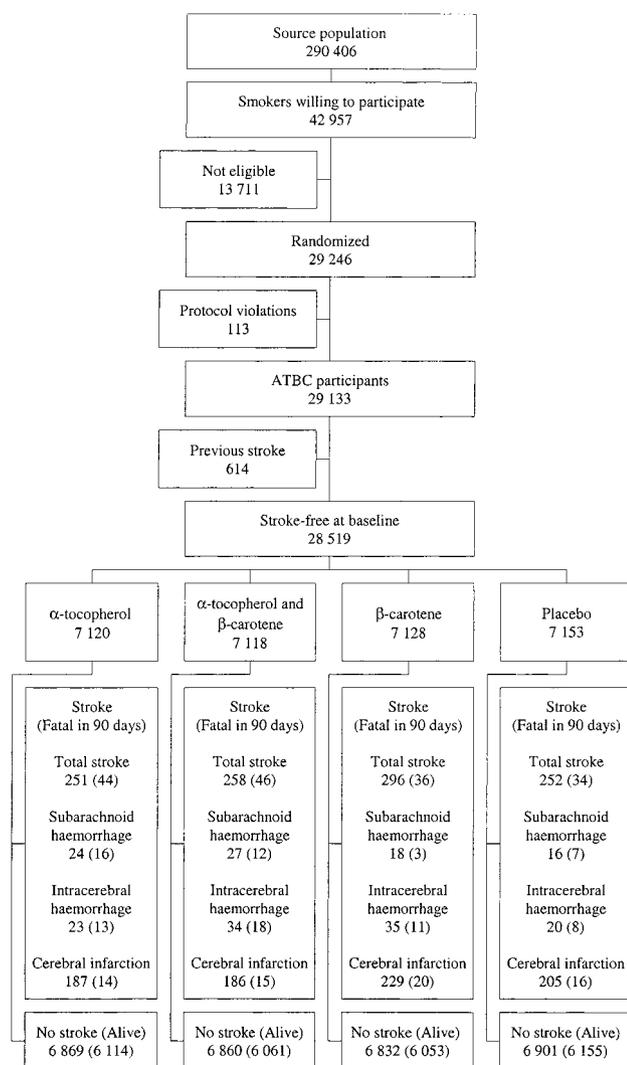


Figure 1. Recruitment, randomization, follow-up, and end points in a controlled trial of middle-aged male smokers (the ATBC Study).

At baseline, the participants completed a questionnaire about their general background, smoking, and medical histories, including a question about physician-diagnosed stroke. A trained study nurse reviewed the questionnaire for accuracy with the participant. The number of cigarettes smoked per day and the duration of smoking habit (in years) were noted, as well as histories of diabetes, hypertension, and heart disease (coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement, and congestive heart failure). The men were given a detailed dietary history (including alcohol consumption) questionnaire,⁸ to be filled at home and returned 2 weeks later at the second baseline visit.

Blood pressure and weight were measured at baseline and annually thereafter. Height was measured at baseline. Body mass index was calculated as weight divided by height squared (kg/m^2). A serum sample was obtained for measuring total cholesterol, α -tocopherol, and β -carotene at baseline and at 3 years. Serum α -tocopherol and β -carotene levels were additionally followed up by continuous sampling. Sera were stored at -70°C . Serum total cholesterol was determined enzymatically (CHOD-PAP method, Boehringer Mannheim). α -Tocopherol and β -carotene levels were determined by high-performance liquid chromatography.⁹

Participants made 3 follow-up visits per year. At each visit, the unused capsules were counted, and compliance was assessed. Overall average compliance, calculated by dividing the total number of unreturned capsules by the number of days active in the trial, was 93%, with no differences between the intervention groups. Only 4% demonstrated poor compliance (ie, took $<50\%$ of the capsules), and practically all of them dropped out of the study during their first trial year. Compliance was correlated with serum levels of α -tocopherol and β -carotene. The dropout rate, including deaths, was 30% (29.8% in the α -tocopherol group, 30.7% in the α -tocopherol and β -carotene group, 31.0% in the β -carotene group, and 30.3% in the placebo group). Twenty-one percent of the men stopped smoking (ie, reported no smoking at ≥ 2 consecutive follow-up visits). The dropout rate and proportion of men who stopped smoking remained even across the 4 intervention groups throughout the follow-up. Also, the means of blood pressure and serum total cholesterol were identical in the trial groups during the follow-up.

One hundred thirteen men were identified after randomization as ineligible because of preexisting cancer, lung cancer diagnosed on the baseline chest x-ray, use of vitamin supplements in excess of the study limits, or nonsmoking. In addition, 614 men reported a history of stroke at the baseline examination. These excluded men were equally distributed among the 4 trial groups. Thus, 28 519 men were included in this study of primary stroke, and their follow-up continued for a median of 6.0 years with a total of 164 225 person-years.

The end point was incident first-on-trial stroke. Strokes were identified by record linkage to the National Hospital Discharge Register and the National Register of Causes of Death, which used the *International Classification of Diseases*, with the 8th edition (ICD-8) used up to the end of 1986 and the 9th edition (ICD-9) used thereafter. The National Hospital Discharge Register uniformly collects information on hospital discharges, including discharge diagnoses, from all hospitals in Finland. The diagnoses in the National Register of Causes of Death are recorded from the death certificates, which are collected nationwide and filed in the central registry of the Statistics of Finland.

ICD-8 and ICD-9 codes 430 to 431, 433 to 434, and 436 were included in the present study; excluded were ICD-8 codes 431.01 and 431.91 denoting subdural hematoma and ICD-9 codes 4330X, 4331X, 4339X, and 4349X representing stenosis or occlusion of precerebral or cerebral arteries without cerebral infarction. Unspecified strokes, ICD code 436, were included in the analyses of all strokes but not in those of stroke subtypes. A stroke was considered fatal if death occurred ≤ 90 days of onset and if stroke was the underlying cause on the death certificate. Based on a validation study using standard diagnostic criteria,¹⁰ the discharge diagnoses of stroke were reliable in the register mentioned above in 90% of all strokes (including unspecified strokes), in 79% of subarachnoid and in 82% of intracerebral hemorrhages, and in 90% of cerebral infarctions.

Statistical analyses were performed according to the intention-to-treat principle. When calculating person-years, follow-up ended at any specific end point of interest, at death, or at the end of the trial, April 30, 1993. No participants were lost from follow-up. Incidence and mortality rates were calculated per 10 000 person-years. Relative risks and their

TABLE 1. Baseline Characteristics by Supplementation Group in a Controlled Trial of Middle-Aged Male Smokers (the ATBC Study)

Characteristics	Supplementation Group			
	α -Tocopherol	No α -Tocopherol	β -Carotene	No β -Carotene
N	14 238	14 281	14 246	14 273
Age, y	57.7	57.7	57.7	57.6
Body mass index, kg/m ²	26.3	26.3	26.3	26.3
Serum total cholesterol, mmol/L	6.23	6.23	6.24	6.23
Alcohol consumption, g/d	18.0	18.1	18.0	18.1
Smoking, cigarettes/d	20.5	20.4	20.4	20.5
Smoking history, y	35.9	35.9	35.9	35.9
Previous diseases, %				
Hypertension	38.7	38.1	38.8	38.0
Heart disease	25.4	24.0	25.0	24.4
Diabetes	4.2	4.1	4.4	3.9
Serum α -tocopherol, mg/L	11.9	11.9	12.0	11.9
Serum β -carotene, mg/L	0.21	0.21	0.21	0.21

Mean values and proportions are given.

95% CIs were estimated by Cox proportional hazards regression. Controlling for potential confounding by adjusting the relative risks by age, body mass index, serum total cholesterol, alcohol, number of cigarettes smoked daily, years of smoking, hypertension, histories of diabetes and heart disease, education, and leisure-time activity had no material influence on the observed effects of α -tocopherol or β -carotene supplementation; thus, the reported relative risks are unadjusted. Interactions between supplements were tested by comparing the log-likelihood tests of the Cox models with and without the interaction term. No interaction was found between the effects of α -tocopherol and β -carotene supplementation on any of the subtypes of stroke or all strokes combined. In further analyses, the effects of the supplements were evaluated independently according to the factorial design, ie, α -tocopherol versus no α -tocopherol, β -carotene versus no β -carotene.

Blood pressure is a significant risk factor for both hemorrhagic and ischemic stroke. Therefore, we examined whether the baseline blood pressure level modified the effect of supplemental α -tocopherol and β -carotene on total stroke. For this, the men were categorized into 4 blood-pressure groups ($\leq 120/80$, 121/81 to 140/90, 141/91 to 160/100, and $>160/100$ mm Hg); if a subject's systolic and diastolic pressures were not in the same category, he was allocated to the higher blood pressure group. Cox regression analyses were made separately in each stratum.

Results

The baseline characteristics in the supplementation groups were practically identical (Table 1). During the median 6.0 years of follow-up, a total of 1057 previously stroke-free men suffered from stroke: 85 men had subarachnoid hemorrhage; 112, intracerebral hemorrhage; 807, cerebral infarction; and 53, unspecified stroke. There were 7 primary strokes among the 113 participants excluded after randomization: 6 cases of cerebral infarction (3 assigned to receive α -tocopherol and β -carotene, 2 assigned to receive β -carotene, and 1 assigned

to receive placebo) and 1 unspecified stroke (assigned to receive α -tocopherol).

During the first 90 days after onset, a total of 201 (19%) men died: 160 (15%) of stroke and 41 of other diseases (13 malignant neoplasms, 16 cardiac deaths, and 12 other causes). The stroke was fatal within 90 days in 45% of patients with subarachnoid hemorrhage or intracerebral hemorrhage but in only 8% of patients with cerebral infarction. Among the 113 men excluded after randomization, only the man with unspecified stroke died ≤ 90 days of onset.

Incident Strokes

The incidence rates of stroke subtypes are shown in Table 2. The risk of subarachnoid hemorrhage was 50% higher ($P=0.07$) but the risk of cerebral infarction was significantly 14% lower ($P=0.03$) in men having α -tocopherol supplementation compared with those without it. There was no effect of α -tocopherol on the risk of intracerebral hemorrhage. β -Carotene had no effect on the risks of subarachnoid hemorrhage and cerebral infarction, but the risk of intracerebral hemorrhage increased 62% ($P=0.01$) compared with those not receiving β -carotene. Neither α -tocopherol nor β -carotene had any significant effect on the risk of all strokes combined. The cumulative frequencies of stroke subtypes by supplementation group are shown in Figure 2.

Fatal Strokes

α -Tocopherol supplementation increased the risk of fatal subarachnoid hemorrhage 181% ($P=0.01$) and of fatal intracerebral hemorrhage 64% ($P=0.09$) (Table 2). β -Carotene supplementation did not change the mortality from any of the subtypes to a statistically significant degree.

Baseline blood pressure level did not modify the effect of supplemental α -tocopherol or β -carotene on total stroke risk. Thus, supplemental α -tocopherol decreased the incidence of total stroke and increased the risk of total fatal stroke similarly in men with baseline blood pressure $<120/80$ mm Hg, $>160/100$ mm Hg, or between these levels.

TABLE 2. Stroke Incidence and Mortality Rates and Relative Risks (95% CI) by Supplementation Group in a Controlled Trial of Middle-Aged Male Smokers (the ATBC Study)

Stroke Subtype and Supplementation Group	Incidence				Mortality*			
	N	Rate per 10 000 Person-Years	Relative Risk	P	N	Rate per 10 000 Person-Years	Relative Risk	P
Subarachnoid hemorrhage								
α -Tocopherol	51	6.2	1.50 (0.97–2.32)	0.07	28	3.4	2.81 (1.37–5.79)	0.005
No α -tocopherol	34	4.1			10	1.2		
β -Carotene	45	5.5	1.13 (0.74–1.73)	0.57	15	1.8	0.65 (0.34–1.25)	0.20
No β -carotene	40	4.9			23	2.8		
Intracerebral hemorrhage								
α -Tocopherol	57	7.0	1.04 (0.72–1.51)	0.84	31	3.8	1.64 (0.93–2.90)	0.09
No α -tocopherol	55	6.7			19	2.3		
β -Carotene	69	8.4	1.62 (1.10–2.36)	0.01	29	3.5	1.39 (0.79–2.44)	0.25
No β -carotene	43	5.2			21	2.5		
Cerebral infarction								
α -Tocopherol	373	45.5	0.86 (0.75–0.99)	0.03	29	3.5	0.81 (0.49–1.32)	0.39
No α -tocopherol	434	52.8			36	4.4		
β -Carotene	415	50.7	1.07 (0.93–1.22)	0.36	35	4.3	1.17 (0.72–1.91)	0.52
No β -carotene	392	47.6			30	3.6		
All strokes								
α -Tocopherol	509	62.1	0.93 (0.83–1.05)	0.25	90	11.0	1.29 (0.94–1.76)	0.11
No α -tocopherol	548	66.6			70	8.5		
β -Carotene	554	67.7	1.11 (0.98–1.25)	0.09	82	10.0	1.06 (0.78–1.44)	0.72
No β -carotene	503	61.1			78	9.5		

Values in parentheses are 95% CIs.

*Indicates the fatal events ≤ 90 days of onset.

Discussion

The ATBC Study protocol specified cardiovascular diseases, including stroke, as secondary end points, with the primary end point of interest being cancer. Randomization was successful, resulting in trial groups with an even distribution of relevant baseline characteristics. The compliance of the participants was excellent, and follow-up was complete. Dropout rate (including deaths), compliance, proportion of men who stopped smoking, and distribution of baseline characteristics remained even across the intervention groups during the follow-up. The large number of participants provides additional assurance that even unknown risk factors were evenly distributed. The end-point assessment, stroke subtyping, was reliable because of the widespread use of computed tomography in Finland. We excluded men after randomization because of protocol violation and history of stroke at baseline, but consequent bias is unlikely because the number of men was small (2%), and they were evenly distributed across the trial intervention groups. The present study included only male smokers; therefore, the results may not be directly generalizable to females and nonsmokers.

The daily α -tocopherol dose was 3-fold and the β -carotene dose 10-fold the daily dietary intakes among the trial participants,⁶ which resulted in a 50% increase of serum α -tocopherol levels and a 17-fold increase of β -carotene levels compared with baseline values. The β -carotene dose can be considered sufficient, whereas the α -tocopherol dose could be considered low for an antioxidant effect on LDL oxidation,¹¹

although even smaller doses of α -tocopherol have been reported to increase the resistance of LDL to oxidation.¹² One quarter of the strokes occurred among dropouts who had not been taking the supplements for at least 5 months before the stroke event. This probably attenuated the observed effects of α -tocopherol and β -carotene supplementation on stroke events.

The median follow-up of 6 years may be too short considering the decades-long development of atherosclerosis in men who have been smoking for, on average, 36 years before the trial but is surely long enough for platelet effects of α -tocopherol to appear. The antiplatelet^{13–15} and anticoagulant¹⁶ actions of vitamin E and its metabolites seem plausible explanations for the higher incidence of subarachnoid hemorrhage and the lower incidence of cerebral infarction in α -tocopherol-supplemented men. This explanation fits well also in our observations of increased fatality of hemorrhagic strokes. Our findings are in accord with a secondary prevention trial report on ischemic stroke in which the combination of vitamin E and aspirin was more effective than aspirin alone.¹⁷ Regarding nonsignificant net effects, α -tocopherol supplementation slightly decreased total stroke incidence and moderately increased total stroke mortality.

β -Carotene supplementation increased, for reasons we do not know, the incidence of intracerebral hemorrhage. We know that β -carotene is easily incorporated into atherosclerotic plaque,^{18,19} but whether its presence renders the plaque and the wall of an atherosclerotic cerebral artery more

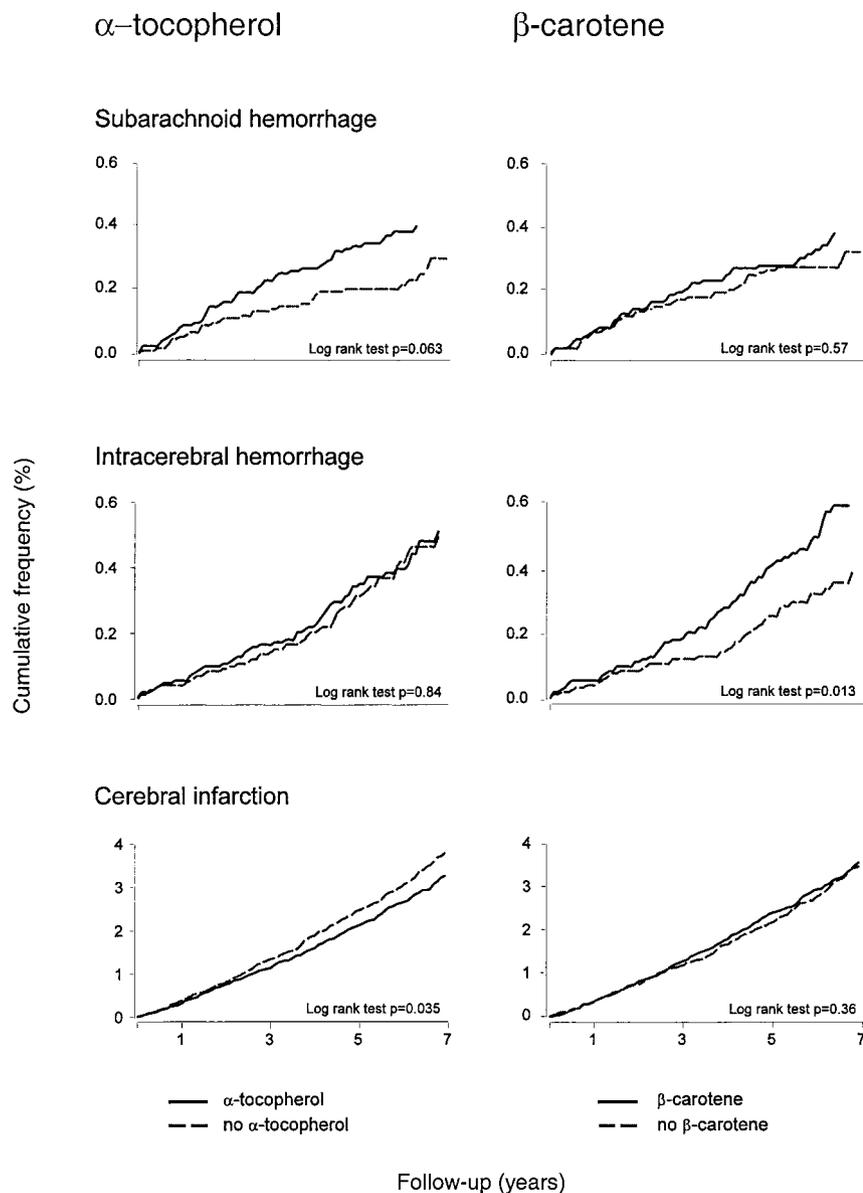


Figure 2. Kaplan-Meier estimates of cumulative frequencies of stroke events among participants who received α -tocopherol compared with those who did not and among participants who received β -carotene compared with those who did not in a controlled trial of middle-aged male smokers (the ATBC Study). Results of the log-rank test for stroke events are presented. Note that the scales for subarachnoid and intracerebral hemorrhages extend to 0.6%, whereas that the scale for cerebral infarction extends to 4.0%.

susceptible to rupture is unknown. Until lately, β -carotene has been considered a very safe substance, but evidence has emerged that it may have harmful effects: it has significantly increased the risk of death from cardiovascular diseases in the Beta-Carotene and Retinol Efficacy Trial (CARET study)²⁰ and the risk of fatal coronary heart disease in men with previous myocardial infarction in the ATBC Study.²¹ β -Carotene supplementation had no effect on total stroke incidence or mortality, which is consistent with results from the Physicians' Health Study,²² in which β -carotene was compared with placebo.

In conclusion, α -tocopherol supplementation decreases the risk of cerebral infarction but increases that of fatal hemorrhagic stroke. The net effect on all strokes is a small decrease in the incidence but a moderate increase in mortality, both of which are nonsignificant and not modified by baseline blood pressure levels. Findings from the ongoing large trials are needed to complete our understanding of the relation of possible beneficial and harmful effects of supplemental α -tocopherol on stroke. Supplemental β -carotene has no preven-

tive effects on stroke but may increase the risk of intracerebral hemorrhage; thus, there is no ground for supplemental β -carotene in stroke prevention.

Acknowledgment

The study was supported by contract N01-CN-45165 from the US National Cancer Institute.

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