Serum lycopene decreases the risk of stroke in men : A population-based follow-up study

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A population-based follow-up study

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ABSTRACT

Objective: Intake of fruits and vegetables and levels of serum carotenoids have been associated with decreased risk of stroke, but the results have been inconsistent. The aim of the present study was to examine whether serum concentrations of major carotenoids, α-tocopherol and retinol, are related to any stroke and ischemic stroke in men.

Methods: The study population consisted of 1,031 Finnish men aged 46–65 years in the Kuopio Ischaemic Heart Disease Risk Factor cohort. Serum concentrations of carotenoids retinol and α-tocopherol were measured by high-performance liquid chromatography. The association between the serum concentrations of lycopene α-carotene, β-carotene, α-tocopherol, and retinol and the risk of strokes was studied by using Cox proportional hazards models.

Results: A total of 67 strokes occurred, and 50 of these were ischemic strokes during a median of 12.1 follow-up years. After adjustment for age, examination year, BMI, systolic blood pressure, smoking, serum low-density lipoprotein cholesterol, diabetes, and history of stroke, men in the highest quartile of serum lycopene concentrations had 59% and 55% lower risks of ischemic stroke and any stroke, compared with men in the lowest quartile (hazard ratio [HR] = 0.45, 95% confidence interval [CI] 0.25–0.95, $p = 0.036$ for any stroke and HR = 0.41; 95% CI 0.17–0.97, $p = 0.042$ for ischemic stroke). α-Carotene, β-carotene, α-tocopherol, and retinol were not related to the risk of strokes.

Conclusions: This prospective study shows that high serum concentrations of lycopene, as a marker of intake of tomatoes and tomato-based products, decrease the risk of any stroke and ischemic stroke in men. ***Neurology*® 2012;79:1540–1547**

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **FINMONICA** = Finnish part of Monitoring of Trends and Determinants in Cardiovascular Diseases; **HPLC** = high-performance liquid chromatography; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases, 9th revision; **KIHD** = Kuopio Ischaemic Heart Disease Risk Factor; **LDL** = low-density lipoprotein; **ROS** = reactive oxygen species; **SBP** = systolic blood pressure.

Under oxidative stress, lipid molecules containing polyunsaturated fatty acids in low-density lipoprotein (LDL) are oxidized, leading to development of chronic diseases (e.g., cardiovascular diseases).[1] Antioxidants, such as carotenoids, inhibit oxidation of LDL by scavenging free radicals and singlet molecular oxygen.[2] Provitamin A carotenoids (e.g., α- and β-carotene) quench singlet oxygen efficiently and interrupt the propagation of the free radical–initiated lipid peroxidation reaction sequence by quenching peroxyl radicals.[3] Carotenoids may affect plaque stability, vasomotor function, and the tendency for thrombosis.[4]

Many previous epidemiologic studies have shown that a high dietary intake of fruits and vegetables rich in carotenoids[5–9] or high serum concentrations of carotenoids are associated with a decreased risk of ischemic stroke or any stroke.[10–12] However, there are studies in which the association between the intake of carotenoids and ischemic stroke is inconsistent.[13,14] No associations between retinol and the risk of ischemic stroke are observed.[10] However, the effect

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of α-tocopherol supplementation on incident of ischemic stroke has been much studied, but the results are inconsistent.[15,16] One possible reason that lycopene might decrease the risk of stroke more than other antioxidants (e.g., α-carotene, β-carotene, or α-tocopherol) may be the consequence of antioxidant activity. Lycopene is a potent antioxidant and the most effective quencher of singlet oxygen,[17] and it was reported to be more effective than β-carotene in cell protection against hydrogen peroxide and nitrogen dioxide radicals.[18] Furthermore, different subtypes of stroke have different etiopathologies[19] and thus most likely also have different associations with dietary antioxidants.[14]

Ischemic stroke accounts for 85% of all strokes.[20] Oxidative stress through formation of reactive oxygen species (ROS) plays a vital role in mediation of neuronal damage during cerebral ischemia. ROS causes membrane phospholipid disruption and results in ischemic cell injury.[21]

The aim of the study was to examine the association of carotenoids retinol and α-tocopherol with ischemic stroke and any stroke in men, because there have been only a few previous studies.

Table 1 Characteristics of participants with or without any stroke (n = 1,031)

	Stroke		
	No (n = 964 [93.5%])	Yes (n = 67 [6.5%])	*p* Value[a]
Demographic characteristics			
Age, y, mean, SD, mean (SD)	56.1 (6.6)	57.9 (6.7)	0.034
BMI, kg/m^2, mean (SD)	27.5 (3.6)	27.7 (4.1)	0.633
SBP, mm Hg, mean (SD)	135 (16)	142 (18)	0.001
Smoking, pack-years, mean (SD)[b]	6.7 (14.3)	7.5 (13.3)	0.646
Current smokers, %	27.0	36.0	0.112
Alcohol intake, g/wk, mean (SD)	78.0 (120.8)	87.6 (138.8)	0.535
Physical activity, kcal/d, mean (SD)	175.1 (207.6)	174.9 (194.4)	0.995
Medical history			
Diabetics, %	6.0	16.0	0.001
History of stroke, %	3.0	3.0	0.954
Laboratory data			
Serum lycopene, μmol/L, mean (SD)	0.16 (0.14)	0.11 (0.11)	0.017
Serum α-carotene, μmol/L, mean (SD)	0.096 (0.077)	0.095 (0.11)	0.898
Serum β-carotene, μmol/L, mean (SD)	0.38 (0.29)	0.37 (0.36)	0.779
Serum α-tocopherol, μmol/L, mean (SD)	28.7 (8.1)	28.1 (5.9)	0.510
Serum retinol, μmol/L, mean (SD)	2.11 (0.46)	2.04 (0.42)	0.223
Serum HDL cholesterol, mmol/L, mean (SD)	1.10 (0.29)	1.07 (0.29)	0.400
Serum LDL cholesterol, mmol/L, mean (SD)	3.93 (0.84)	3.97 (0.95)	0.677
Serum triglycerides, mmol/L, mean (SD)	1.62 (1.04)	1.68 (0.99)	0.640

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.
[a] The χ^2 statistic was used for categorical variables and 1-way analysis of variance for continuous variables.
[b] Pack-years denote the lifelong exposure to smoking, estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.

METHODS

Study population. The analyses were performed with the participants of the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study, a longitudinal population-based study designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes. The study population is a representative sample of men living in the city of Kuopio and its surrounding rural communities, who were 42−61 years of age at baseline.[22] The baseline examinations of the present study were performed between 1991 and 1993. Of 1,229 potentially eligible men, 1,038 (83%) volunteered to participate in baseline examinations, 107 declined to participate, and 52 were not able to participate because of illness, relocation, or death. The participants with no missing data were eligible for the present study. Men with a previous history of stroke (n = 32) were excluded. Concentrations of carotenoids retinol and α-tocopherol were available for 1,031 men, who remained in the study.

Standard protocol approvals, registrations, and patient consents. The KIHD Study was approved by the Research Ethics Committee of the University of Kuopio, and each participant gave written informed consent.

Laboratory analyses. Blood specimens were collected in Terumo Venoject vacuum tubes (10 mL) (Terumo, Tokyo, Japan) from the antecubital vein without tourniquet after an overnight fast. Subjects had rested in a supine position for 30 minutes before blood sampling. Subjects were instructed to abstain from consuming alcohol for 3 days and from smoking for 12 hours before blood collection. Serum for carotenoids and other biochemical measurements was frozen immediately after separation at −80°C. Concentrations of serum retinol, α-tocopherol, and carotenoids were measured by high-performance liquid chromatography (HPLC) as described previously.[23] Mean interassay coefficients of variation varied from 11.0 to 16.2%. Concentrations of serum total, LDL, and high-density lipoprotein cholesterol and triglycerides were assayed with enzymatic methods as described earlier.[23]

Other measurements. Resting blood pressure was measured in the morning by 2 trained nurses with a random-zero mercury sphygmomanometer (Hawksley, Lancing, United Kingdom). After the subjects had rested in a supine position for 5 minutes, 6 measurements were taken at 5-minute intervals: 3 while the subjects were in a supine position, 1 while the subjects were standing, and 2 while the subjects were sitting. The mean of all 6 measurements was used as the systolic blood pressure (SBP) and diastolic blood pressure. Body mass index (BMI) was computed as the ratio of weight (kilograms) to the square of height (meters). Alcohol consumption was assessed with a structured quantity-frequency method on drinking behavior over the previous 12 months. Physical activity was assessed by using a 12-month leisure-time history based on self-reported information about frequency per month over the preceding year, average duration per occasion, and intensity level. Metabolic units were

assigned for each activity according to intensity.[24] Information on diabetes and smoking was collected with a self-administered questionnaire and checked by the interviewer. Diabetes mellitus was defined as a fasting blood glucose level ≥6.7 mmol/L or as a clinical diagnosis of diabetes with dietary, oral, or insulin treatment. A subject was defined as a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or a pipe within the past 30 days. The lifelong exposure to smoking was estimated as the product of the number of smoking years and the number of tobacco products smoked daily at the time of examination

Ascertainment of follow-up events. Incident strokes between 1991 and 1992 were ascertained through the Finnish part of Monitoring of Trends and Determinants in Cardiovascular Diseases (FINMONICA) stroke register.[25,26] Information on stroke incidence between 1993 and December 31, 1999, was obtained by computerized linkage to the Finnish national hospital discharge registry and death certificate registers. Diagnostic information was collected from hospitals and classified by a neurologist with diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were hospital documents, death certificates, autopsy reports, and medicolegal reports. The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting >24 hours (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke (International Classification of Diseases [ICD]-9 codes 430−439 and ICD-10 codes I60–I68 and G45–G46) was classified into 1) a definite stroke, 2) no stroke, or (3) an unclassifiable event. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerized national hospital discharge and death registers. Definite strokes and unclassifiable events were included in the group of any stroke. Each definite stroke was classified into 1) an ischemic stroke (ICD-9 codes 433−434; ICD-10 code I63) or 2) a hemorrhagic stroke (ICD-9 codes 430−431; ICD-10 codes I60–I61). If the subject had multiple nonfatal strokes during follow-up, the first stroke was considered as the end point. CT was performed in 90% of the patients by 1993, and CT, MRI, and autopsy reached 100% by 1997. Every resident of Finland has a unique personal identifier that is used in registers. There were no losses to follow-up.

Statistical analysis. Continuous variables are presented as means (SDs) and categorical variables are presented as percentages. Means of the continuous variables were compared using analysis of variance, and χ^2 tests were used for categorical variables. The relationship between variables and demographic-clinical characteristics associated with serum lycopene were analyzed with Pearson correlation coefficients. Tests of linear trend were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. Subjects were classified into quartiles according to their serum concentrations of antioxidants. Hazard ratios (HRs) and 95% confidence intervals (CIs) for strokes in quartiles of plasma concentrations of antioxidants were analyzed by using a Cox proportional hazards model. Covariates were selected on the basis of their previously established role as a predictive factor on the basis of overall evidence and available data.[10] Thus, risk

Table 2 Demographic characteristics of the study population by categories of lycopene, aged 46−65 years (n = 1,031)

	Quartile of lycopene				
	≤0.03 μmol/L (n = 258)	0.04−0.12 μmol/L (n = 244)	0.13−0.22 μmol/L (n = 270)	>0.22 μmol/L (n = 259)	*p* for heterogeneity[a]
Demographic characteristics					
Age, y, mean, SD, mean (SD)	58.7 (6.0)	57.2 (6.4)	55.5 (6.8)	53.5 (6.2)	<0.001
BMI, kg/m^2, mean (SD)	27.7 (3.9)	27.8 (4.0)	27.7 (3.5)	27.0 (3.1)	0.079
SBP, mm Hg, mean (SD)	138 (17)	136 (17)	136 (17)	132 (15)	0.001
Smoking, pack-years, mean (SD)	10.9 (18.4)	6.2 (13.6)	4.7 (11.4)	5.4 (11.7)	<0.001
Current smokers, %	36.0	25.0	24.0	25.0	0.008
Alcohol intake, g/wk, mean (SD)	70.6 (142.9)	72.6 (116.0)	79.0 (112.1)	92.0 (114.2)	0.183
Physical activity, kcal/d, mean (SD)	147.4 (157.6)	172.2 (229.8)	175.4 (221.8)	205.1 (207.6)	0.017
Medical history					
Diabetics, %	8.0	6.0	7.0	6.0	0.698
History of stroke, %	5.0	3.0	2.0	2.0	0.064
Laboratory data					
Serum α-carotene, μmol/L, mean (SD)	0.082 (0.060)	0.086 (0.074)	0.10 (0.084)	0.11 (0.090)	<0.001
Serum β-carotene, μmol/L, mean (SD)	0.31 (0.19)	0.33 (0.22)	0.41 (0.35)	0.49 (0.36)	<0.001
Serum α-tocopherol, μmol/L, mean (SD)	27.2 (7.5)	28.7 (8.1)	28.5 (7.3)	30.4 (8.6)	<0.001
Serum retinol, μmol/L, mean (SD)	2.04 (0.46)	2.09 (0.44)	2.15 (0.47)	2.15 (0.44)	0.015
Serum HDL cholesterol, mmol/L, mean (SD)	1.08 (0.29)	1.09 (0.31)	1.10 (0.29)	1.12 (0.26)	0.299
Serum LDL cholesterol, mmol/L, mean (SD)	3.99 (0.89)	3.87 (0.80)	3.87 (0.85)	4.00 (0.84)	
Serum triglycerides, mmol/L, mean (SD)	1.70 (1.18)	1.68 (1.03)	1.59 (0.94)	1.51 (1.00)	0.171

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; KIHD = Kuopio Ischemic Heart Disease Risk Factor; LDL = low-density lipoprotein; SBP = systolic blood pressure.
[a] Analysis of variance.

factors or covariates were chosen based on their clinical relevance. The multivariable-adjusted models included age, examination year, BMI, SBP, smoking, serum LDL cholesterol, diabetes, and history of stroke. Tests for statistical significance were 2-sided, and differences with $p < 0.05$ were considered statistically significant. SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

RESULTS The median follow-up time to strokes or the end of follow-up was 12.1 years (range 0.03−13.8 years), 12,475 person-years. There were 50 subjects (4.8%) with ischemic stroke and 67 subjects with any stroke (6.5%). Table 1 shows the baseline characteristics of the subjects. Compared with participants with any stroke, those without any stroke were older, had higher SBP, had lower concentrations of serum lycopene, and had higher incidence of diabetes. Smokers had lower levels of lycopene ($p = 0.045$), α-carotene ($p < 0.001$), β-carotene ($p = 0.001$), and α-tocopherol ($p = 0.002$) compared with nonsmokers. Table 2 shows the baseline characteristics of the subjects categorized by quartiles of serum lycopene. Men who had lycopene >0.22 μmol/L, compared with those in the lowest categories, were younger, had lower SBP, smoked less, performed higher physical activity, and had higher concentrations of carotenoids α-tocopherol and retinol.

Pearson correlation coefficients were calculated to assess the relation between carotenoids and possible risk factors for stroke-associated risk factors. Cases of stroke tended to increase with age ($r = 0.07$, $p = 0.034$), SBP ($r = 0.10$, $p = 0.001$), and diabetes ($r = 0.10$, $p = 0.001$), whereas cases decreased with increasing concentrations of lycopene ($r = -0.08$, $p = 0.017$). Carotenoids correlated with each other and with retinol and α-tocopherol. Lycopene correlated with α-carotene ($r = 0.16$, $p < 0.001$), β-carotene ($r = 0.25$, $p < 0.001$), retinol ($r = 0.09$, $p = 0.005$), and α-tocopherol ($r = 0.14$, $p < 0.001$). β-Carotene correlated strongly with α-carotene ($r = 0.61$, $p < 0.001$) and retinol with α-tocopherol ($r = 0.31$, $p < 0.001$).

Demographic and clinical characteristics associated with serum lycopene were assessed by use of Pearson correlation coefficients. Age, BMI, SBP,

Table 3 HRs and 95% CIs of any stroke according to quartiles of carotenoids by using the Cox proportional hazards model in the KIHD Study (n = 1,031)

	Quartiles of carotenoids				
	1 (lowest)	2	3	4 (highest)	p Value[a]
Serum lycopene, μmol/L	≤0.030	0.040-0.12	0.13-0.22	>0.22	
No. of cases/no. of total	25/258	15/244	16/270	11/259	
HR1 (95% CI)[b]	1.0[c]	0.58 (0.30-1.10)	0.57 (0.30-1.08)	0.45 (0.22-0.93)	0.032
HR2 (95% CI)[d]	1.0[c]	0.60 (0.31-1.14)	0.55 (0.29-1.06)	0.45 (0.21-0.95)	0.036
Serum α-carotene, μmol/L	≤0.050	0.060-0.090	0.10-0.13	>0.13	
No. of cases/no. of total	20/271	22/279	14/234	11/247	
HR1 (95% CI)[b]	1.0[c]	1.15 (0.61-2.15)	0.85 (0.42-1.72)	0.61 (0.28-1.30)	0.197
HR2 (95% CI)[d]	1.0[c]	1.23 (0.65-2.33)	0.94 (0.46-1.92)	0.63 (0.29-1.37)	0.241
Serum β-carotene, μmol/L	≤0.22	0.23-0.32	0.33-0.46	>0.46	
No. of cases/no. of total	24/248	12/276	15/252	16/255	
HR1 (95% CI)[b]	1.0[c]	0.42 (0.21-0.83)	0.57 (0.30-1.09)	0.57 (0.30-1.09)	0.084
HR2 (95% CI)[d]	1.0[c]	0.41 (0.21-0.84)	0.65 (0.33-1.27)	0.62 (0.31-1.23)	0.170
Serum retinol, μmol/L	≤1.78	1.79-2.06	2.07-2.37	>2.37	
No. of cases/no. of total	19/259	19/260	16/256	13/256	
HR1 (95% CI)[b]	1.0[c]	1.07 (0.56-2.02)	0.96 (0.48-1.87)	0.76 (0.37-1.56)	0.462
HR2 (95% CI)[d]	1.0[c]	0.96 (0.50-1.84)	0.93 (0.47-1.84)	0.67 (0.33-1.38)	0.277
Serum α-tocopherol, μmol/L	≤23.4	23.5-27.4	27.5-32.2	>32.2	
No. of cases/no. of total	13/259	18/258	20/255	16/259	
HR1 (95% CI)[b]	1.0[c]	1.48 (0.72-3.02)	1.57 (0.78-3.15)	1.23 (0.59-2.57)	0.582
HR2 (95% CI)[d]	1.0[c]	1.42 (0.68-2.97)	1.43 (0.68-3.05)	1.08 (0.48-2.44)	0.861

Abbreviations: BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; KIHD = Kuopio Ischemic Heart Disease Risk Factor; LDL = low-density lipoprotein; SBP = systolic blood pressure.
[a] Obtained from a Cox proportional hazards model.
[b] Adjusted for age and examination year.
[c] Reference value.
[d] Adjusted for model 1 and BMI, SBP, smoking, serum LDL cholesterol, diabetes, and history of stroke.

smoking, and history of stroke were inversely associated with serum lycopene, whereas physical activity was positively associated.

Serum concentrations were analyzed from the same men (n = 845) during the 7 years follow-up (1998–2001) to figure out changes in dietary habits. The concentration of lycopene increased from the baseline (0.16 vs 0.20 μmol/L, $p < 0.001$). Conversely, α-tocopherol and β-carotene concentrations remained at the same level, whereas the concentration of retinol decreased (2.12 vs 1.92 μmol/L, $p < 0.001$). There were no data on concentration of α-carotene during the follow-up.

Table 3 shows the relation of baseline serum concentrations of carotenoids retinol and α-tocopherol to the risk of any stroke, and Table 4 shows the relation to the risk of ischemic stroke. After adjustment for age and examination year, high serum lycopene concentrations decreased the risk of any stroke and ischemic stroke. After multivariable adjustment for age, examination year, BMI, SBP, smoking, serum LDL cholesterol, diabetes, and history of stroke, men in the highest quartile of serum lycopene concentrations as compared with men in the lowest quartile had 55% and 59% lower risks of any stroke and ischemic stroke (HR = 0.45, 95% CI 0.25–0.95, $p = 0.036$ for any stroke and HR = 0.41, 95% CI 0.17–0.97, $p = 0.042$ for ischemic stroke). The cumulative incidence of any stroke by quartiles of lycopene is shown in the figure. The incidence of any stroke was least in the highest quartile of lycopene. Concentrations of α-carotene, β-carotene, α-tocopherol, and retinol were not related to the risk of strokes.

DISCUSSION In this prospective cohort study, high serum lycopene concentrations may decrease the risk of any stroke and ischemic stroke in men. No association was found with concentrations of α-carotene, β-carotene, α-tocopherol, and retinol and any stroke.

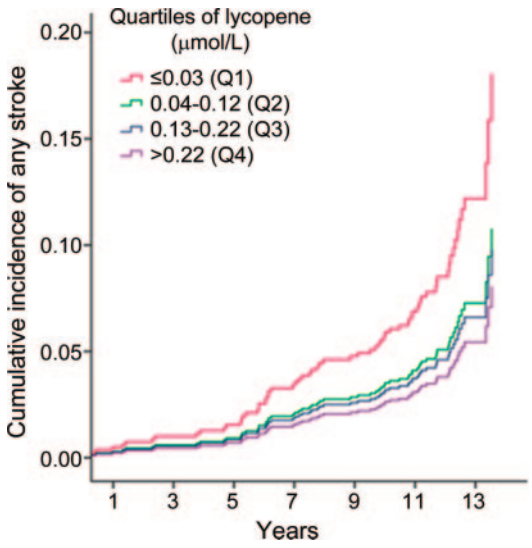
Serum concentrations of α-carotene and β-carotene of this cohort were roughly similar to those found in

Table 4 HRs and 95% CIs of ischemic stroke according to quartiles of carotenoids by using the Cox proportional hazards model in the KIHD Study (n = 1,031)

	Quartiles of carotenoids				
	1 (lowest)	2	3	4 (highest)	*p* Value[a]
Serum lycopene, μmol/L	≤0.030	0.040–0.12	0.13–0.22	>0.22	
No. of cases/no. of total	20/258	11/244	11/270	8/259	
HR1 (95% CI)[b]	1.0[c]	0.53 (0.25–1.11)	0.49 (0.23–1.04)	0.42 (0.18–0.98)	0.045
HR2 (95% CI)[d]	1.0[c]	0.54 (0.26–1.14)	0.48 (0.22–1.02)	0.41 (0.17–0.97)	0.042
Serum α-carotene, μmol/L	≤0.050	0.060–0.090	0.10–0.13	>0.13	
No. of cases/no. of total	15/271	18/279	10/234	7/247	
HR1 (95% CI)[b]	1.0[c]	1.29 (0.63–2.65)	0.83 (0.36–1.89)	0.52 (0.21–1.32)	0.172
HR2 (95% CI)[d]	1.0[c]	1.38 (0.66–2.86)	0.91 (0.39–2.10)	0.52 (0.20–1.34)	0.176
Serum β-carotene, μmol/L	≤0.22	0.23–0.32	0.33–0.46	>0.46	
No. of cases/no. of total	17/248	9/276	12/252	12/255	
HR1 (95% CI)[b]	1.0[c]	0.44 (0.19–0.98)	0.64 (0.31–1.35)	0.59 (0.28–1.25)	0.169
HR2 (95% CI)[d]	1.0[c]	0.42 (0.19–0.96)	0.69 (0.32–1.50)	0.61 (0.27–1.37)	0.224
Serum retinol, μmol/L	≤1.78	1.79–2.06	2.07–2.37	>2.37	
No. of cases/no. of total	13/259	14/260	13/256	10/256	
HR1 (95% CI)[b]	1.0[c]	1.17 (0.55–2.50)	1.17 (0.54–2.54)	0.88 (0.38–2.04)	0.771
HR2 (95% CI)[d]	1.0[c]	1.09 (0.51–2.35)	1.16 (0.53–2.54)	0.78 (0.34–1.82)	0.570
Serum α-tocopherol, μmol/L	≤23.4	23.5–27.4	27.5–32.2	>32.2	
No. of cases/no. of total	10/259	14/258	12/255	14/259	
HR1 (95% CI)[b]	1.0[c]	1.50 (0.67–3.39)	1.21 (0.52–2.80)	1.40 (0.62–3.18)	0.415
HR2 (95% CI)[d]	1.0[c]	1.38 (0.60–3.17)	1.03 (0.42–2.52)	1.09 (0.44–2.73)	0.854

Abbreviations: BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; KIHD = Kuopio Ischemic Heart Disease Risk Factor; LDL = low-density lipoprotein; SBP = systolic blood pressure.
[a] Obtained from a Cox proportional hazards model.
[b] Adjusted for age and examination year.
[c] Reference value.
[d] Adjusted for model 1 and BMI, SBP, smoking, serum LDL cholesterol, diabetes, and history of stroke.

Figure Cumulative incidence of any stroke by quartiles of lycopene during follow-up



Cumulative incidence of any stroke by quartiles (Q) of serum lycopene concentrations (Q1, ≤0.030 μmol/L; Q2, 0.040–0.12 μmol/L; Q3, 0.13–0.22 μmol/L; and Q4, >0.22 μmol/L). The Cox proportional hazards model adjusted for age, examination year, body mass index, systolic blood pressure, smoking, serum low-density lipoprotein cholesterol, diabetes, and history of stroke.

the Japanese population,[11] whereas lycopene concentrations were at the same level as those found in the population of Taiwan.[12] In the Finnish Botnia Dietary study, it was shown that an 0.82-mg intake of lycopene calculated from 3 days of estimated food records corresponds to 0.31 μmol/L as blood levels[27,] which is as high as the level in the Japanese population.[11] This study suggests that it is possible in Finland to reach serum lycopene concentrations as high as those in other populations.[11] However, there are no recommendations for intake of carotenoids, because carotenoids are not indicated to be essential nutrients for humans, unlike vitamin A.[28] There are no corresponding data on intake of tomato or tomato-based products in Finland. However, in a multicenter study it was observed that tomato intake varies between 18.4 and 163.6 g/day, corresponding to 0.50–1.31 μmol/L as plasma lycopene.[29] Serum concentrations of lycopene, α-carotene, and β-carotene were lower among current smokers as has been reported previously.[30,31]

There are only a few previous studies that examined the association between concentrations of blood carotenoids and the risk of any stroke and ischemic stroke. It has been reported that high serum concentrations of lycopene, α-carotene, β-carotene, and total carotenes were related to lower risk of stroke.[10–12] Furthermore, previous studies have evaluated associations between dietary intake of fruits and vegetables or carotenoids and the risk of strokes. Most of these studies have observed a protective effect against strokes,[5–9] but some studies had not.[13,14,32] In a meta-analysis, an increased fruit and vegetable intake was associated with a reduced risk of stroke. Results support the recommendations to consume more than 5 servings of fruits and vegetables per day, which is likely to cause a major reduction in strokes.[33] Conflicting findings may be due to difficulties in estimating intake of carotenoids or inadequate food frequency questionnaire data.[34] Although an inverse association between α-tocopherol supplementation and stroke has been observed in previous studies,[15] we did not find an association between α-tocopherol concentrations and ischemic stroke. Meta-analysis consisting of 9 randomized, placebo-controlled trials α-tocopherol increased the risk for hemorrhagic stroke by 22% and reduced the risk of ischemic stroke by 10%.[15] In another meta-analysis of 13 randomized controlled trials, α-tocopherol supplementation did not protect from stroke.[16] Consistent with a previous study,[10] the association between retinol and ischemic stroke was not observed. The reason may be that retinol levels are highly regulated and vary only slightly with intake.[35]

Studies have reported that lycopene has many bioactive functions. Beside its antioxidant properties, it reduces inflammation, inhibits cholesterol synthesis, improves immune function,[36–38] and prevents platelet aggregation and thrombosis[39] and thereby may decrease the risk of stroke. Besides lycopene, provitamin A carotenoids (e.g., α- and β-carotene) quench efficiently singlet oxygen and interrupt the propagation of the free radical–initiated lipid peroxidation reaction sequence by quenching peroxyl radicals.[3]

Analyses in the present study are based on the baseline measurement of serum carotenoids retinol and α-tocopherol. Serum concentrations were analyzed from the same men during the follow-up to clarify changes in dietary habits. We observed that the concentration of lycopene increased during follow-up, but the concentration of retinol decreased. The same HPLC method was used at the baseline and during the follow-up. It is possible that after the diagnosis of stroke men had increased amounts of tomatoes or tomato-based products in their diet, which may explain the increased concentration of lycopene.

The strengths of this study include its prospective population-based design, completed follow-up (no losses), and reliable assessments of incident strokes. A primary limitation is that few stroke cases occurred in this cohort, which limits the statistical power. It was not possible to perform statistical analyses separately for smokers and nonsmokers because of the few

cases. Residual confounding may be a potential source of bias in this study, most notably due to the lack of information on dietary behaviors in the participants. Other limitations were that we included variables of smoking at the baseline in the model, but we cannot exclude the possibility of residual confounding due to smoking, e.g., related to change of smoking habits after the baseline. Because blood samples were collected at baseline when all men were stroke-free, these concentrations do not represent any changes made after diagnosis. Therefore, it is impossible to know whether patients had changed their lifestyles and dietary habits by increasing intake of dietary antioxidants after ischemic stroke diagnosis. Information on food and nutrient intake was not included in our cohort.

Results of the present study show that high serum concentrations of lycopene, as a marker of intake of tomatoes and tomato-based products, decrease the risk of any stroke and ischemic stroke in men. Thus, a balanced diet including fruits and vegetables may prevent stroke.

AUTHOR CONTRIBUTIONS

J. Karppi: I am responsible for submitting the manuscript and for all communications with the journal throughout the review process. I ensure that all authors have approved revised versions of the manuscript before initial submission and also before submission of revisions and that all authors sign the disclosure agreement. I have participated in study design, statistical analysis. and writing of the manuscript. J.A. Laukkanen: He obtained the funding, participated in the study design, and commented on the manuscript. J. Sivenius: He classified the strokes in the study population. K. Ronkainen: He performed statistical analyses and participated in interpretation of data. S. Kurl: He participated in the study design and commented on the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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Thank you, Dr. John F. Kurtzke!

The Neurology online archive has recently been updated to include the following seminal articles related to early research in MS:

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis; ACTH vs placebo in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–10.

Rose AS, Kuzma JW. A protocol for a cooperative study to evaluate the therapeutic effectiveness of ACTH on multiple sclerosis in acute exacerbations. Neurology 1968 (June); 18 (6 Part 2): 1–20 + study forms.

Rose AS, Kuzma JW, Kurtzke, JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs. placebo – final report. Neurology 1970 (May); 20 (5 Part 2) 1–59.

Kurtzke, JF. Multiple Sclerosis: What's in a name? Neurology 1988;38:309–316.

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