Serum lycopene concentrations and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study[1–3]

Tiina H Rissanen, Sari Voutilainen, Kristiina Nyyssönen, Riitta Salonen, George A Kaplan, and Jukka T Salonen

ABSTRACT

Background: Interest in lycopene is growing rapidly following the recent publication of epidemiologic studies in which high circulating lycopene concentrations were associated with reductions in cardiovascular disease. Lycopene is one of the major carotenoids in the Western diet and is probably one of the protective factors in a vegetable-rich diet.

Objective: We studied the hypothesis that the intima-media thickness of the common carotid artery (CCA-IMT) would be greater in men with low serum lycopene concentrations.

Design: We investigated the relation between serum lycopene concentration and CCA-IMT in 1028 middle-aged men (aged 46–64 y) in eastern Finland who were participants in the Kuopio Ischaemic Heart Disease Risk Factor study and who were examined in 1991–1993. The subjects were classified into quarters according to serum lycopene concentration.

Results: In a covariance analysis with adjustment for covariates, the men in the lowest quarter of serum lycopene concentration had a significantly higher mean CCA-IMT and maximal CCA-IMT ($P = 0.005$ and $P = 0.001$ for the difference, respectively) than did the other men. The mean and maximal CCA-IMT increased linearly across the quarters of serum lycopene concentration.

Conclusions: A low serum lycopene concentration is associated with a higher CCA-IMT in middle-aged men from eastern Finland. This finding suggests that the serum lycopene concentration may play a role in the early stages of atherosclerosis. Increased thickness of the intima-media has been shown to predict coronary events; thus, lycopene intakes and serum concentrations may have clinical and public health relevance. *Am J Clin Nutr* 2003;77:133–8.

KEY WORDS Lycopene, atherosclerosis, carotid arteries, intima-media thickness, carotenoids, Kuopio Ischaemic Heart Disease Risk Factor study, middle-aged men

INTRODUCTION

Nutrition plays an important role in the development of coronary artery disease (CAD). Diets rich in fruit and vegetables containing carotenoids are of interest because of their potential health benefit against chronic diseases such as CAD and cancer. Increased intakes and tissue or blood concentrations of carotenoids are associated with a reduced risk of cardiovascular disease (1–6). Although β-carotene has been investigated for many years, lycopene, the acyclic form of β-carotene, has attracted substantial interest more recently. Lycopene is a red pigment and is one of the major carotenoids in Western diets. In contrast with most other carotenoids, however, which are widely distributed among a great variety of fruit and vegetables, lycopene intake comes predominantly from tomatoes and tomato products. Lycopene has unique structural and chemical features that may contribute to its specific biological properties (7). The antioxidant properties of lycopene are resistant to heat and cooking, and the bioavailability of lycopene in processed tomato products is higher than that in unprocessed, fresh tomatoes.

Lycopene is an antioxidant carotenoid without provitamin A activity and has been shown to be a more potent antioxidant than α- or β-carotene (8). The oxidation-protecting effect of lycopene and tomatoes has been shown in both human and animal studies (9, 10). A reduced oxidative modification of LDL may be one of the mechanisms by which lycopene reduces the risk of CAD and atherosclerotic progression (11, 12).

Only a few previous studies addressed the association between low concentrations of circulating lycopene and early atherosclerosis. We tested the hypothesis that the intima-media thickness of the common carotid artery (CCA-IMT) would be greater in men with low serum lycopene concentrations.

SUBJECTS AND METHODS

Subjects

The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study is an ongoing, population-based study designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes in middle-aged men from eastern Finland, a population with one of the highest recorded rates of CAD (13). The study was approved by the Research Ethics Committee of the

University of Kuopio, and all study subjects gave their written informed consent.

A total of 2682 men aged 42, 48, 54, or 60 y were enrolled in the study between March 1984 and December 1989. Four-year reexaminations of those examined in 1987–1989 were conducted between March 1991 and December 1993. For the reexaminations, the subjects visited the study site twice, with an interval of 7 d. Blood pressure was measured at the first visit, and CCA-IMT was scanned and blood samples were drawn at the second visit. Of a total of 1229 men eligible for the reexamination, 52 had died, had severe illness, or had moved away from the region, and 139 could not be contacted or refused to participate. High-resolution ultrasound examinations of CCA-IMT and data on serum lycopene concentrations were available for 1028 men. These results make up the cross-sectional data of the reexamination of the KIHD follow-up study.

Ultrasonographic assessment of the intima-media thickness of the common carotid artery

CCA-IMT was assessed by high-resolution B-mode ultrasonography of the right and left CCAs at the distal end, proximal to the carotid bulb. The ultrasound equipment (Biosound Phase 2; Biosound Inc, Indianapolis) was equipped with a high-resolution probe. Images were focused on the posterior wall of the right and left CCAs and were recorded on videotape for image analysis. The ultrasonographic examinations were carried out by well-trained ultrasound technicians and were performed after the subjects had rested in a supine position for 15 min.

IMT measurements were made through computerized analysis of the videotaped ultrasound images with PROSOUND software (University of Southern California, Los Angeles). This software uses an edge-detection algorithm, specifically designed for use with ultrasound imaging, that allows automatic detection, tracking, and recording of the intima-lumen and media-adventitia interfaces, estimated at ≈100 points, in both the right and left CCAs in a 1.0–1.5-cm section (14). For the present study, 2 measures of IMT were used. Mean IMT was computed as the mean of ≈100 IMT measurements in the right CCA and another 100 measurements in the left CCA. Maximum IMT was computed as the average of the points of maximum thickness from the right and left CCAs, which is indicative of the depth of intrusion of the IMT into the lumen in this part of the CCA.

A separate study concerning the intra- and interobserver variability of IMT measurements was carried out in 10 randomly chosen middle-aged men who had participated in the KIHD study. The between-observer CV was 10.5% for the first assessments by 4 observers for both the right and left CCAs. The correlation coefficients ranged from 0.90 to 0.99. The intraobserver variability (reproducibility) was described by the absolute value of difference between the first and the third measurement by each observer. The mean absolute difference was 0.087 mm, which is 8.1% of the mean of all measurements (15).

Measurements

The subjects came to give blood samples between 0800 and 1000. They were instructed to abstain from ingesting alcohol for 3 d and from smoking and eating for 12 h before the blood sampling. After the subjects had rested in a supine position for 30 min, blood was drawn with Terumo Venoject vacuum tubes (Terumo, Tokyo). No tourniquet was used.

Serum for lycopene, β-carotene, and α-tocopherol measurements was extracted with ethanol and hexane, and the measurements were made with the use of a reversed-phase HPLC method in samples that had been stored at $-80\,°C$ for 4–36 mo (16). This method cannot separate lycopene isomers. The detection limit for lycopene with this method was 0.03–0.07 μmol/L. Values below the limit of detection of the assay were marked as 0.00 in the statistical analysis. The CV was determined with a serum pool analyzed in 25 separate batches. The CVs were 11.0% for lycopene and 16.2% for β-carotene. To evaluate the stability of lycopene, we calculated the means of the first 56 samples stored for 36 mo (0.113 μmol/L) and the means of the last 56 samples stored for 4 mo (0.110 μmol/L). Thus, serum lycopene samples were well preserved, and the difference in storage times did not attenuate the results.

Lipoproteins were separated from fresh serum samples by combined ultracentrifugation ($100\,000 \times g$, $4\,°C$, 23 h) and precipitation. Concentrations of serum total, LDL, and HDL cholesterol (Kone Instruments, Espoo, Finland) and of serum triacylglycerols (Boehringer Mannheim, Mannheim, Germany) were determined enzymatically with an autoanalyzer (Kone Specific; Kone Instruments) (17). Serum folate was determined by radioimmunoassay (Bio-Rad, Hercules, CA) (18).

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 min, 6 measurements were taken at 5-min 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 and diastolic blood pressure.

A subject was defined a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or a pipe within the past 30 d. The number of cigarettes, cigars, and pipefuls of tobacco currently smoked daily and the duration of regular smoking in years were recorded on a self-administered questionnaire that was checked by an interviewer.

Body weight was measured by using a balance scale. During the height and weight measurements, the subjects wore light clothing and no shoes. Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m^2).

Statistical analysis

Data were analyzed by using SPSS statistical software (version 10.0 for WINDOWS; SPSS Inc, Chicago). Mean age; BMI; systolic and diastolic blood pressure; serum triacylglycerols; serum HDL, LDL, and total cholesterol; and serum folate, β-carotene, and α-tocopherol are reported as means ± SDs. Cigarette smoking is reported as a percentage. Subjects were classified into quarters according to their serum concentration of lycopene: < 0.04, 0.04–0.12, 0.13–0.22, and > 0.22 μmol/L). The statistical significance of the differences between these lycopene groups in the main characteristics of the subjects was studied by using one-way analysis of variance (ANOVA). The correlations between CCA-IMT and nutritional factors and cardiovascular disease risk factors were estimated by Spearman's correlation coefficients.

The association between serum concentrations of lycopene and ultrasonographically assessed CCA-IMT was tested for statistical significance by using covariance analysis. Three different sets of covariates were used: model 1 included age, ultrasound observer, and examination years; model 2 included model 1 and systolic blood pressure, serum HDL and LDL cholesterol, and smoking; and model 3 included model 2 and serum triacylglycerols, BMI,

TABLE 1
Characteristics of the subjects[1]

| | Quarter of serum lycopene (μmol/L) | | | | P for heterogeneity[2] |
	<0.04	0.04–0.13	0.14–0.22	>0.22	
Age (y)	58.7 ± 6.0[3]	57.2 ± 6.4	55.5 ± 6.8	53.5 ± 6.2	<0.001
Systolic blood pressure (mm Hg)	138.1 ± 16.7	136.7 ± 16.8	132.9 ± 17.4	132.0 ± 15.0	0.001
BMI (kg/m²)	27.7 ± 3.9	27.6 ± 4.0	27.5 ± 3.5	26.8 ± 3.1	0.048
Serum lycopene (μmol/L)	0.00 ± 0.00	0.09 ± 0.02	0.17 ± 0.03	0.34 ± 0.12	—
Serum β-carotene (μmol/L)	0.31 ± 0.18	0.40 ± 0.22	0.40 ± 0.36	0.51 ± 0.36	<0.001
Serum folate (nmol/L)	9.44 ± 3.81	10.01 ± 3.76	10.53 ± 4.08	11.34 ± 4.64	<0.001
Serum α-tocopherol (μmol/L)	27.2 ± 0.2	28.7 ± 0.2	28.5 ± 0.2	30.4 ± 0.2	<0.001
Serum total cholesterol (mmol/L)	5.57 ± 0.97	5.51 ± 0.92	5.44 ± 0.94	5.58 ± 0.92	0.284
Serum LDL cholesterol (mmol/L)	3.99 ± 0.89	3.87 ± 0.80	3.87 ± 0.85	4.00 ± 0.84	0.128
Serum HDL cholesterol (mmol/L)	1.08 ± 0.29	1.09 ± 0.31	1.10 ± 0.29	1.12 ± 0.26	0.299
Serum triacylglycerols (mmol/L)	1.70 ± 1.18	1.68 ± 1.03	1.59 ± 0.94	1.51 ± 1.00	0.171
Smokers (%)	36	25	24	26	0.011

[1] $n = 1028$.
[2] ANOVA.
[3] $\bar{x} \pm$ SD.

and 3 nutritional factors (serum folate, β-carotene, and α-tocopherol). All tests were two-tailed, and P values <0.05 were considered significant.

RESULTS

The mean concentration of serum lycopene was 0.15 ± 0.14 μmol/L, ranging from below the detection limit to 1.02 μmol/L. The main characteristics of the subjects are presented in **Table 1**. Serum β-carotene, folate, and α-tocopherol concentrations; age; systolic blood pressure; BMI; and smoking differed significantly between the subjects in different quarters of serum lycopene concentration. Serum lycopene concentrations were higher in the younger (aged 46–55 y) men than in the older (aged >55 y) men (0.19 and 0.11 μmol/L, respectively, $P < 0.001$, ANOVA) and were non-significantly higher in nonsmokers than in smokers (0.16 and 0.14 μmol/L, respectively, $P = 0.07$, ANOVA).

Serum lycopene concentrations correlated negatively with mean and maximal CCA-IMT (Spearman's correlation coefficients: $r = -0.22$, $P < 0.001$, and $r = -0.20$, $P < 0.001$, respectively). The strongest correlations were found between mean CCA-IMT and age, systolic blood pressure, BMI, serum LDL cholesterol, and serum lycopene (**Table 2**). Except for the relation with serum lycopene, all of these relations were positive.

In a covariance analysis, we observed a significant inverse association between serum concentrations of lycopene and mean and maximal CCA-IMT. In model 1, men in the lowest quarter of serum lycopene concentration had significantly higher mean ($P < 0.001$ for the difference) and maximal ($P < 0.001$ for difference) CCA-IMT than did the other men. Additional adjustment for other covariates (model 2) did not change the observed results ($P = 0.001$ and $P < 0.001$ for the difference, respectively). Furthermore, a similar inverse trend remained in model 3 ($P = 0.005$ and $P = 0.001$ for the difference, respectively). The increments in the mean and maximal CCA-IMT were linear across the quarters of serum lycopene concentration. The P values for the linear trend for mean and maximal CCA-IMT in model 1 were 0.001 and < 0.001, respectively. In model 2, the corresponding P values were 0.006 and 0.002, respectively, and in model 3 they were 0.039 and 0.013, respectively. In all models, the mean and maximal CCA-IMT decreased linearly across the quarters of serum lycopene concentration (**Table 3**).

The association between serum lycopene concentration and CCA-IMT was stronger in smokers than in nonsmokers. In model 2, the mean and maximal CCA-IMT decreased nonlinearly across the quarters of serum lycopene in smokers (mean CCA-IMT: 0.95, 0.88, 0.84, and 0.86 mm, P for linear trend across the quarters = 0.003; maximal CCA-IMT: 1.33, 1.24, 1.15, and 1.21 mm, P for linear trend across the quarters = 0.002). In nonsmokers the association between serum concentrations of lycopene and mean and maximal CCA-IMT was weaker and nonsignificant but linear (mean CCA-IMT: 090, 0.88, 0.88, and 0.85 mm, P for linear trend across the quarters = 0.159; maximal CCA-IMT: 1.25, 1.21, 1.21, and 1.17 mm, P for linear trend across the quarters = 0.098). In the fully adjusted model (model 3), both mean and maximal CCA-IMT were 10% higher ($P = 0.002$ and $P = 0.002$ for the difference, respectively) in smokers in the lowest quarter of serum lycopene than in the other smokers. Additional adjustment for smoking years did not significantly change the results.

DISCUSSION

High circulating concentrations of carotenoids are presumed to protect against atherosclerosis before its clinical manifestation

TABLE 2
Spearman's correlation coefficients (r) and statistical significance for the association between mean intima-media thickness of the common carotid artery and nutritional factors and cardiovascular disease risk factors in middle-aged eastern Finnish men

	r	P
Age (y)	0.43	<0.001
Systolic blood pressure (mm Hg)	0.29	<0.001
BMI (kg/m²)	0.14	<0.001
Serum lycopene (μmol/L)	−0.22	<0.001
Serum β-carotene (μmol/L)	−0.07	0.020
Serum folate (nmol/L)	−0.06	0.051
Serum α-tocopherol (μmol/L)	−0.06	0.046
Serum total cholesterol (mmol/L)	0.09	0.004
Serum LDL cholesterol (mmol/L)	0.14	<0.001
Serum HDL cholesterol (mmol/L)	−0.11	<0.001
Serum triacylglycerols (mmol/L)	0.11	<0.001
Smoking (cigarettes/d × y of smoking)	0.04	0.192

TABLE 3
Adjusted mean and maximal (and 95% CI) intima-media thickness of the common carotid artery (CCA-IMT) by quarter of serum lycopene concentration in the 3 models[1]

| | Quarter of serum lycopene (μmol/L) | | | | |
	<0.04	0.04–0.13	0.14–0.22	>0.22	P for linear trend[2]
	mm				
Model 1					
Mean CCA-IMT	0.92 (0.89, 0.95)	0.88 (0.85, 0,90)	0.87 (0.85, 0.89)	0.85 (0.83, 0.88)	<0.001
Maximal CCA-IMT	1.28 (1.25, 1.32)	1.21 (1.18, 1.24)	1.20 (1.16, 1.23)	1.18 (1.15, 1.22)	<0.001
Model 2					
Mean CCA-IMT	0.92 (0.89, 0.94)	0.88 (0.85, 0.90)	0.87 (0.85, 0.89)	0.86 (0.83, 0.88)	0.012
Maximal CCA-IMT	1.27 (1.24, 1.31)	1.21 (1.18, 1.25)	1.20 (1.17, 1.23)	1.19 (1.15, 1.22)	0.014
Model 3					
Mean CCA-IMT	0.91 (0.89, 0.93)	0.87 (0.85, 0.90)	0.87 (0.85, 0.90)	0.86 (0.84, 0.89)	0.039
Maximal CCA-IMT	1.27 (1.23, 1.30)	1.21 (1.18, 1,24)	1.20 (1.17, 1.23)	1.19 (1.16, 1.23)	0.013

[1] Model 1 was adjusted for age, examination years, and ultrasound observer; model 2 was adjusted for model 1 variables plus smoking, systolic blood pressure, and serum HDL- and LDL-cholesterol concentrations; model 3 was adjusted for model 2 variables plus serum triacylglycerols, body mass index, and serum α-tocopherol, folate, and β-carotene.
[2] Covariance analysis.

(19–23). The main finding of the present study is that low serum lycopene concentrations are associated with early atherosclerosis, as manifested as an increased thickness of the CCA in middle-aged men from eastern Finland.

The association between blood concentrations or dietary intakes of lycopene and thickness of the artery wall was studied earlier in very few studies (**Table 4**). In our previous Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study (19), low plasma concentrations of lycopene were associated with CCA-IMT 18% higher than that in men with plasma concentrations of lycopene higher than the median. In women, the difference was nonsignificant after the adjustments. In a subsample of the Atherosclerosis Risk in Communities (ARIC) study (20), there were 231 age-, sex-, race-, and field center–matched case-control pairs. An increased serum concentration of lycopene was associated with nonsignificantly lower odds of being a case after adjustment for risk factors (odds ratio: 0.81). In the same study (21), a high dietary intake of provitamin A carotenoids was associated with a lower prevalence of carotid plaques and a lower thickness of the artery wall, although these associations were not statistically significant. In the ARIC study, the dietary intake of lycopene was not assessed. In the Rotterdam study (22), serum lycopene was the only carotenoid that was associated with a decreased risk of aortic atherosclerosis in current and former smokers.

In the Etude sur le Vieillissement Artériel (23), subjects in the highest quarter of plasma total carotenoids had lower CCA-IMT, but this association became nonsignificant after adjustment for common risk factors. In men, the prevalence of carotid plaques decreased linearly across the quarters of plasma carotenoid concentration ($P < 0.016$). Plasma concentrations of lycopene were not measured in that study.

The prevalence of carotid plaques and increased thickness of the intima media has been shown to predict coronary events (27, 28). The association between blood or tissue concentrations of lycopene and risk of CAD was studied earlier in several studies. In the multicenter EURAMIC study (6), low adipose tissue concentrations of lycopene were associated with greater risk of a myocardial infarction. In a nested case-control study from Washington County (26), excess risk of myocardial infarction was associated with low serum concentrations of lycopene, but a protective

association with higher concentrations of lycopene was suggested in smokers. In the prospective Massachusetts Health Care Panel study (29), a high dietary intake of total carotenoids was associated with a reduced risk of fatal myocardial infarction and cardiovascular disease death. We also found in the KIHD study that men with low serum concentrations of lycopene had a higher risk of an acute coronary event or stroke than did men with higher serum lycopene concentrations (25).

The oxidative modification of LDL particles may play a role in the formation of foam cells, atherosclerotic lesions, and CAD (11, 30). Men who have high titers of autoantibodies against oxidatively modified LDL and those with elevated serum 7β-hydroxycholesterol concentrations have accelerated progression of carotid atherosclerosis (11, 12). Antioxidants can inhibit the oxidative modification of LDL, may retard atherosclerotic progression, and, consequently, may prevent clinical complications of atherosclerosis such as myocardial infarction (31, 32). Lycopene and other carotenoids have been shown to act as antioxidants (7, 8, 10, 33). This action is probably due to the ability of carotenoids to quench singlet oxygen, a potential initiator of lipid peroxidation (33). Lycopene exhibits the highest physical quenching rate of all carotenoids (8). It has also been shown that serum concentrations of lycopene are inversely correlated with serum thiobarbituric acid–reactive substances (TBARS) (34), an indicator of lipid peroxidation. Both LDL-TBARS and conjugated dienes were lowered significantly by dietary lycopene supplementation (10). Other mechanisms through which lycopene may inhibit atherosclerosis include intercellular gap junction communication and hormonal and immune system modulation (34). In addition, in cell culture, lycopene is the most effective carotenoid at suppressing adhesion molecule and monocyte adhesion to endothelial cells (35).

The mean CCA-IMT in our subjects was somewhat higher than that reported in most other studies (20, 23, 28, 36). This is consistent with the high incidence of clinical CAD in eastern Finland. The mean serum lycopene concentration in our study was much lower than that reported in most other population-based studies from European countries, in which lycopene concentrations were 2–4-fold higher than in our study (2, 24). In an American population, circulating concentrations of lycopene were even 6-fold greater than those in our study (20). In only one earlier study (22)

TABLE 4
Studies of the association of circulating and tissue concentrations of lycopene with the risk of cardiovascular disease and atherosclerosis[1]

Study, publication year, and nationality of subjects	Type of study	Sex of subjects	n	Variables	Sample of lycopene	Mean (±SD) concentration	Findings
ARIC study, Iribarren et al, 1997 (20): American	Nested case-control	F, M	462	IMT	Serum	Cases: 0.89 ± 0.43; controls: 0.91 ± 0.42 μmol/L	Nonsignificantly lower odds of being a case with increases in lycopene
Rotterdam study, Klipstein-Grobush et al, 2000 (22): Dutch	Case-control	F, M	216	Plaques of the abdominal aorta	Serum	Cases: 0.12 ± 0.09; controls: 0.13 ± 0.09 μmol/L	Nonsignificantly lower odds ratio in the highest quarter compared with the lowest. Significant odds ratio in smokers: 0.35 (0.13–0.94)
Bruneck study, D'Orico et al, 2000 (24): Italian	Cross-sectional and prospective, 5-y follow-up	F, M	392	Prevalence and incidence of carotid plaques	Serum	0.53 ± 0.34 to 0.76 ± 0.49 μmol/L	Lycopene did not significantly predict the risk of atherosclerosis
ASAP study, Rissanen et al, 2000 (19): Finnish	Cross-sectional	F, M	520	IMT	Plasma	Men: 0.14 ± 0.12; women: 0.17 ± 0.11 μmol/L	In men, significantly lower adjusted IMT with plasma concentration of lycopene higher than the median
KIHD study, Rissanen et al, 2000 (25): Finnish	Prospective, 5.3 y follow-up	M	725	Acute coronary event and stroke	Serum	0.17 ± 0.14 μmol/L	Adjusted relative risk = 0.30 (0.16−0.59) in 3 highest quarters compared with the lowest quarter
Street et al, 1994 (26): American	Nested case-control, 14 y follow-up	F, M	369	MI	Serum	Cases: 39.0 ± 18.6; controls: 40.2 ± 18.8 μg/dL	Nonsignificantly lower serum lycopene concentration in cases than in controls. Excess risk of MI in smokers with serum concentration of lycopene lower than the median
EURAMIC study Kohlmeier et al, 1997 (6): multicenter	Case-control	M	1379	MI	Adipose tissue	0.21–0.36 μg/g	Adjusted odds ratio = 0.52 (0.33–0.82) in the 10th compared with the 90th percentile
Linköping-Vilnius Coronary Disease Risk Assessment Study, Kristenson et al, 1997 (2): Swedish and Lithuanian	Cross-sectional	M	210	CAD mortality	Plasma	Linköping: 0.62; Vilnius: 0.33 μmol/L	Lower plasma concentration of lycopene and higher risk of CAD mortality in Vilnius than in Linköping

[1] ARIC, Atherosclerosis Risk in Communities; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; CAD, coronary artery disease; IMT, intima-media thickness; KIHD, Kuopio Ischaemic Heart Disease Risk Factor; MI, myocardial infarction.

were mean circulating concentrations of lycopene parallel to those in the present study. The most likely explanation for this is the low dietary intake of lycopene in Finland. In the Finnish Mobile Clinic Health Examination Survey (37), the daily intake of lycopene was 0.9 mg for women and 0.7 mg for men, whereas the intake of lycopene is 1.3 mg in Spain (38) and as high as 6.6 mg in the United States (39). Our study subjects had low concentrations of lycopene, and the association was stronger at low concentrations, which may explain the strength of the relation. One explanation for the weak effect found in some studies with high tissue concentrations and more homogeneous concentrations of lycopene may be the lack of low circulating concentrations of lycopene.

It is possible that the serum concentration of lycopene is an indicator for other beneficial dietary factors. However, the effect of lycopene was significant after adjustment for other plant-derived nutrients, serum folate, β-carotene, and α-tocopherol. Smokers and older men had lower serum concentrations of lycopene than did nonsmokers and younger men. This could either be due to differences in dietary intake or be a consequence of smoking or aging itself. We adjusted statistical models for age and smoking status to eliminate the effect of these factors. An adjustment for smoking attenuated but did not abolish the association between lycopene and CCA-IMT. However, the association between serum concentrations of lycopene and CCA-IMT seemed to be stronger in smokers than in nonsmokers.

The results of previous studies of the association between blood concentrations of lycopene and atherosclerosis or cardiovascular disease in smokers and nonsmokers are inconsistent. Our results support the findings of the Rotterdam study (22) and the nested case-control study from Washington County (26). In contrast, in the EURAMIC (6) and the ASAP (19) studies, there was a stronger effect of lycopene on myocardial infarction and atherosclerosis among nonsmokers. Smoking is a well-known risk factor for CAD. Smokers have been shown to have lower plasma concentrations of most carotenoids, but results concerning blood concentrations of lycopene according to smoking status are mixed (40). The relation between lycopene and smoking is incompletely understood, and more knowledge is needed to clarify this association.

In conclusion, the results of the present study show that low serum concentrations of lycopene are associated with higher CCA-IMT in middle-aged men from eastern Finland. A higher IMT has been shown to predict coronary events (27, 28); thus, our finding suggests that serum concentrations of lycopene, a biomarker of tomato-rich food intake, may play a role in the early stages of atherogenesis and may have clinical and public health relevance.

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