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Relation of Lycopene Intake and Consumption of Tomato Products to Incident Cardiovascular Disease

Paul F. Jacques[1], **Asya Lyass**[2,3], **Joseph M. Massaro**[4], **Ramachandran S. Vasan**[2,5], and **Ralph B. D'Agostino Sr**[2,3]

[1]Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111, USA

[2]NHLBI Framingham Heart Study, 73 Mt. Wayte Avenue, Framingham, MA 01702, USA

[3]Department of Mathematics and Statistics, College of Arts and Sciences, Boston University, 111 Cummington Street, Boston MA 02215 USA

[4]Department of Biostatistics, School of Public Health, Boston University, 715 Albany Street, Boston, MA 02118 USA

[5]Department of Medicine, School of Medicine, Boston University, 761 Harrison Avenue, Boston, MA 02118 USA

Abstract

Evidence for cardioprotective effects of lycopene is inconsistent. Studies of circulating lycopene generally report inverse associations with cardiovascular disease (CVD) risk, but studies based on lycopene intake do not. The failure of the dietary studies to support the findings based on biomarkers may be due in part to misclassification of lycopene intakes. To address this potential misclassification, we used repeated measures of intake obtained over 10 years to characterize the relation between lycopene intake and incidence of CVD (n=314), coronary heart disease (CHD, n=171) and stroke (n=99) in the Framingham Offspring Study. Hazards ratios (HR) for incident outcomes were derived from Cox proportional hazards regression models using logarithmically transformed lycopene intake adjusted for CVD risk factors and correlates of lycopene intake. HRs were interpreted as the increased risk for a 2.7-fold difference in lycopene intake, a difference approximately equal to its inter-quartile range. Using an average of three intake measures with a 9 year follow-up, lycopene intake was inversely associated with CVD incidence (hazards ratio (HR): 0.83, 95% confidence interval (CI): 0.70-0.98). Using an average of two intake measures and 11 years of follow-up, lycopene intake was inversely associated with CHD incidence (HR: 0.74, 95% CI: 0.58-0.94). Lycopene intake was unrelated to stroke incidence. Our study of lycopene intake and CVD provides supporting evidence for an inverse association between lycopene and CVD risk

Send Correspondence to: Paul F Jacques, USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111 USA, paul.jacques@tufts.edu, Phone: 617 556 3322, Fax: 617 556 3344.

None of the authors has a conflict of interest to declare.

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but additional research is needed to determine if lycopene or other components of tomatoes, the major dietary source of lycopene, are responsible for the observed association.

Keywords

lycopene; cardiovascular disease; coronary heart disease; stroke

Introduction

Individuals who consume higher amounts of vegetables and fruits consistently demonstrate lower risks of cardiovascular disease (CVD)[1-4], but there is still much that we do not understand regarding the mechanism relating vegetable and fruit intake to CVD risk. Accumulating evidence from intervention trials suggests that the protective effect of vegetables and fruits may not necessarily be a consequence of their vitamin E and β-carotene[5], whereas other research has suggested that lycopene, a dietary carotenoids obtained largely from tomato products, may provide cardioprotective benefits[6-9]. Many[6-9], but not all[10-12], prospective studies relating circulating lycopene concentrations and CVD risk report inverse associations, while studies based on dietary intake generally failed to detect significant independent associations between lycopene and CVD risk[13-17]. The reason for the failure of the dietary studies to support the findings based on biomarkers is not known but may be due, in part, to misclassification of lycopene intakes.

To address the potential misclassification, we used repeated measures of intake obtained over 10 years to characterize the relation between intake of lycopene and tomato-based products and the incidence of CVD, coronary heart disease (CHD) and stroke.

Research Design and Methods

Population description

The Framingham Heart Study began in 1948 with the enrollment of 5,209 adults aged 28-62 residing in Framingham, a town west of Boston, Massachusetts[18] and has continued for over 60 years, with the survivors returning every two years for a physical examination and to complete a series of questionnaires, laboratory and cardiovascular tests. By 1971, the original cohort included 1,644 husband-wife pairs and 378 individuals who had developed CVD. The offspring of these subjects and the offspring's spouses were invited to participate, and 5,135 of the 6,838 eligible individuals participated in the first Framingham Offspring Study examination[19]. The Offspring cohort undergoes repeat examination approximately every 3-4 years. For the present study we used data derived from the 5th, 6th, and 7th study examinations, which spanned 10 years (1991-2001), with follow-up for incident CVD through 2008.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human participants were approved by the Boston University Medical Center Institutional Review Board. Written informed consent was obtained from all participants. The current study was approved by the Tufts Medical Center Institutional Review Board.

Dietary Assessment

Dietary intakes were assessed using the Harvard semi-quantitative food frequency questionnaire (FFQ)[20,21] at the 5th, 6th, and 7th examinations. The FFQ consists of a list of foods with a standard serving size and a selection of 9 frequency categories ranging from never or <1 serving/month to ≥ 6 servings/day. Participants were asked to report their frequency of consumption of each food item during the past year. Participants could also add up to three additional foods that are important components of their diets but are not listed on the questionnaire. Information on nutrient supplement use was also obtained by the FFQ. Dietary information was judged as unreliable and excluded from further study if reported energy intakes are <2511 kJ/d (600 kcal/d) or >16743 kJ/d (4000 kcal/d) for women and > 17580 kJ (4200 kcal/d) for men or if more than twelve food items were left blank.

Lycopene intake from food sources and multivitamin supplements was used to calculate lycopene intake. Ketchup, a relatively concentrated source of lycopene, was not listed as a standard food item on the FFQ, but participants had the option of listing it as an additional food. We also created a measure of tomato product consumption as the sum of tomatoes, tomato juice, tomato sauce and pizza consumption measured as servings per week.

The lycopene intake from the FFQ has been previously validated against plasma lycopene concentrations[22] and intake of tomatoes have been validated using repeated diet records[23,24]. Correlations between lycopene intake based on the FFQ and plasma lycopene were 0.47 and 0.21 for non-smoking men and women, respectively. The lower correlation in women was believed to be a result of hormonal factors affecting circulating lycopene concentrations and not the result of a difference in the ability of the FFQ to capture lycopene intake in men and women[22,25]. The correlation between intake of tomatoes based on the FFQ and four 7-day diet records for the corresponding time period was 0.73 in women[24] while the correlation in men based on two 7-day diet records was 0.71[23].

Ascertainment of CVD events and Deaths

All participants are under continuous surveillance for the occurrence of CVD events and death. Hospitalization records and physician office visit records are obtained and reviewed by a committee of three experienced investigators. For each death, the same committee assigns an underlying cause of death based on Framingham Heart Study records, hospitalization records, and when available, autopsy results[26]. Criteria for the diagnoses of cardiovascular events have been described elsewhere[27]. Incident CVD includes CHD (recognized or unrecognized myocardial infarction, angina pectoris, coronary insufficiency, and CHD death), cerebrovascular disease (stroke and transient ischemic attack), congestive heart failure (by Framingham criteria), and peripheral vascular disease (intermittent claudication). An unrecognized myocardial infarction was considered to have occurred if there was electrocardiographic evidence of significant loss of R waves or appearance of pathologic Q waves on serial tracings in the absence of a clinically recognized event. Sudden death, defined as death occurring within one hour of onset of symptoms, is attributed to CHD unless another cause is apparent[26]. Stroke was defined as an acute-onset focal neurological deficit of presumed vascular origin persisting for ≥24 hours. Transient ischemic attack was defined as an episode of rapid-onset focal neurological dysfunction

attributed to focal cerebral ischemia with resolution within 24 hours. All cerebrovascular events all were adjudicated by a panel of 2 neurologists[28]. For intermittent claudication, a physician-administered standardized questionnaire was used to elicit subjective symptoms of calf discomfort with exertion that occurred sooner with uphill or fast-paced walking and was alleviated with rest. All suspected claudication events were verified independently by a second physician examiner.

Assessment of covariates

Covariates used in our analyses included sex, age, systolic blood pressure, total cholesterol, total cholesterol/HDL ratio, body mass index (BMI), current smoking status, number of packs smoked per day, hypertension treatment, prevalent diabetes, and dietary intakes of energy, saturated fat, β-carotene, flavonols, vitamin C and vitamin E. Medical history (e.g. medication use) and lifestyle activities (e.g. smoking history) were assessed during a standardized medical examination and interview. Height and weight were measured with the participant standing, shoes off, and wearing only a hospital gown. BMI was calculated as body weight in kilograms divided by the square of height in meters. Sitting blood pressure was measured twice on each participant after a 5-minute rest using a random-zero sphygmomanometer and two readings were averaged for the analyses. Fasting (≥8 hours) blood samples were drawn for assessing the levels lipids. Plasma total cholesterol was measured by an enzymatic method[29], and HDL cholesterol was measured after dextran-magnesium precipitation[30]. Diabetes was defined as a plasma glucose level ≥7.0 mmol/L (fasting) or ≥11.1 mmol/L (non-fasting) or use of hypoglycemic drug therapy. We included β-carotene, flavonols, vitamin C and vitamin E as covariates not only as markers of vegetable and fruit consumption but also because these represent potential bioactive compounds found in varying quantities in tomatoes and other lycopene-containing foods.

Statistical Methods

Our primary exposure was the natural logarithm of lycopene intake. Our primary outcome was incident CVD. Secondary analyses considered intake of tomatoes and tomato-based products as an additional exposure and incident CHD and stroke as outcomes. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

Hazards ratios (HR) derived from Cox proportional hazards regression models (SAS PROC PHREG) was used to characterize the prospective associations between lycopene and tomato product intakes and risk of CVD. Because lycopene intake was transformed using a natural logarithm, the HR is interpreted as the relative risk for a 2.7-fold difference (i.e., a 1 unit difference on the natural logarithm scale) in lycopene intake. The 2.7-fold difference represents a reasonable intake difference in this population. It is similar to the ratio between the 75th and 25th percentiles of lycopene intake assessed at the 5th, 6th and 7th examinations, which ranged from 2.4 to 2.6.

In an attempt to minimize misclassification of lycopene and tomato product intake data, we considered two different exposures based on an average of intakes from the 5th and 6th examinations and the 5th, 6th and 7th examinations. For each of these exposures, we initiated

follow-up for CVD events at the date of the last examination included in the averaged intake. For example, follow-up for the averaged intake for the 5th and 6th examinations started at the date of the examination for participants at their 6th examination. Thus, the 6th examination served as baseline for the averaged intakes from the 5th and 6th examinations and the 7th examination as baseline for the averaged intakes from the 5th, 6th and 7th examinations.

We considered three different models based on inclusion of covariates: 1) an age and sex adjusted model (Model 1), 2) a model with additional adjustment for systolic blood pressure, total cholesterol, total cholesterol/HDL ratio, BMI, smoking, number of packs per day, hypertension treatment, prevalent diabetes, saturated fat intake and energy intake (Model 2), and 3) a model with additional adjustment for dietary factors including beta-carotene, vitamin C, vitamin E and flavonol intakes (Model 3). Covariates, like the dietary data, reflect average values at the respective baseline examinations for the two follow-up periods.

To assess the validity of the proportional hazards assumption, we introduced interaction terms between follow-up time and our exposures, and use likelihood ratio tests to assess evidence for departures from this assumption. There was no evidence that this assumption was violated for any of these models. We also examine the potential for effect modification by sex and smoking, but there was no evidence of any statistical interactions.

The numbers of participants available for follow up was dependent on the baseline examination. Participation at the baseline examination was the initial criteria for inclusion. Among those participating in the 6th examination, 412 participants were excluded because of existing CVD, 313 because of missing or invalid dietary data, and 131 because of missing covariate data, leaving 2,667 participants for follow-up. At the 7th examination, 479 participants were excluded because of existing CVD, 406 because of missing or invalid dietary data, and 121 because of missing covariate data, leaving 2,525 participants for follow-up.

Results

The average age and body mass index at the 5th examination was 54 years and 27.2 kg/m^2. Fifty-six percent of the participants were women, 18% were current smokers, and 16% and 5% had a history of hypertension and diabetes, respectively. Mean lycopene intake was 7.6, 7.9 and 8.0 mg/d at the 5th, 6th and 7th examinations and mean consumption of tomatoes and tomato-based products was 4.4, 4.4 and 4.6 servings/wk at these three examinations.

The main contributors to lycopene intake at the 5th study examination were tomato sauce (46.4%), pizza (23.6%), fresh and canned tomatoes (14.6%), tomato juice (6.0%), watermelon (5.7%), and grapefruit and grapefruit juice (2.6%). No other food item contributed more than 1%. There was a modest shift in sources of lycopene by the 7th examination where tomato sauce remained the predominant contributor to lycopene intake (45.1%), followed by fresh and canned tomatoes (26.1%), pizza (12.4%), watermelon (7.4%), tomato juice (5.9%) and grapefruit and grapefruit juice (2.3%).

The median follow-up was approximately 11 years from the 6th examination and approximately 9 years from the 7th examinations. Although there were no statistically significant associations observed between lycopene intake and CVD incidence using the average of two intake assessments from 5th and 6th examinations (Table 1), we observed significant associations between lycopene intake based on the average of three measures from the 5th, 6th and 7th examinations and CVD after adjustment for CVD risk factors (models 2) and additional adjustment for dietary correlates of lycopene intake (model 3). Interpretation of the HRs from these models is complicated by the natural logarithm transformation of lycopene intake. For example, the HR for model 3 based on the average intake from the 5th, 6th and 7th examinations (HR= 0.83) would translate into a 17% lower incidence of CVD for a 2.7-fold difference in lycopene intake. The 2.7-fold difference is similar to the ratio between the 75th and 25th percentiles of lycopene intake assessed at the 5th, 6th and 7th examinations.

The evidence for a relation between lycopene intake and overall CHD shows a slightly different pattern than CVD (Table 1). We observed that increasing intake of lycopene based on the average of intakes from the 5th and 6th examinations was associated with a significantly lower risk of CHD, but the association between lycopene intake and CHD based on the average of the 5th, 6th and 7th examination and the shorter follow-up period was not statistically significant. The association based on the average of the 6th and 7th examinations remained significant after multivariate adjustment. The HR of 0.74 for model 3 would translate into a 26% lower incidence of CHD for a 2.7 fold difference in lycopene intake. No significant associations were observed between lycopene intake and stroke (Table 1).

The relationship between tomato and tomato product consumption and CVD and CHD were very similar to those seen with lycopene consumption (Table 1), except the relation between tomato product consumption and CHD was also apparent when using the intakes averaged from three examinations. The tomato products included in this analysis accounted for approximately 90% of lycopene intake. As with lycopene intake, we observed no associations between tomato and tomato product consumption and risk of stroke.

Discussion

These present findings demonstrate an inverse association between lycopene intake and risk of CHD, but not stroke and, along with evidence from with earlier studies relating serum lycopene to risk of CVD[6-9] and carotid artery intima-media thickness[31,32], provide support for the hypothesis that higher lycopene is associated with lower CVD risk. In contrast, the previous studies of dietary lycopene and CVD risk provided little evidence of any association[13-17]. One of these studies based on male smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial reported an inverse association with two subtypes of stroke (cerebral infarction and intracerebral hemorrhage) but lycopene intakes in this cohort were very low (median intake of 0.59 mg/d)[16], complicating the interpretation of this finding. There was no significant association observed between lycopene intake and CVD risk in the Women's Health Initiative, but, in agreement with our observations, there was a marginally-significant 31% reduction in risk of CHD associated with an approximately 5-

fold difference in lycopene intakes from the lowest to the highest intake quintile categories[14]. The failure to detect a significant association may be the consequence of potential bias introduced by misclassification of exposure because lycopene intake was assessed using one baseline measure and then participants were followed for a median follow-up of 7.2 years. Misclassification is a less likely explanation for the failure to see significant associations in two other studies as lycopene intake was updated using cumulative averages during follow-up[13,15]. The final study to examine the relationship between dietary lycopene and CVD is a retrospective case-control study, which is subject to more sources of bias, including misclassification of lycopene intake as intake was based on a single assessment[17].

We also observed inverse associations between consumption of tomatoes and tomato products and CVD and CHD incidence. The aforementioned Women's Health Initiative study, which found no significant association between lycopene intake and CVD risk, reported significant inverse associations between consumption of tomato products and CHD and total CVD[14].

We did not observe any evidence of an association between stroke incidence and either lycopene intake or tomato product consumption. However, given the relatively small number of events, particularly for the analyses based on the average of three intake measures, it is possible that the failure to see any relation with stroke was a consequence of inadequate statistical power.

Bioavailability and absorption of lycopene are relatively low and depend on the processing and preparation of the lycopene-containing foods and on the fat content of the meal in which lycopene is consumed[33-36]. Low and variable bioavailability and absorption will result in greater misclassification of actual lycopene exposures based on intake making it more difficult to establish relations between intake and health outcomes. Although the use of multiple measures of lycopene intake would not limit misclassification associated with bioavailability, our ability to characterize lycopene intake using repeated measures of intake may have allowed us to limit variability from other sources increasing our ability to detect associations with CVD risk.

In addition to the use of multiple measures of dietary intake, the present study has other strengths, most notably the use of the Framingham Heart Study Offspring cohort, a preeminent longitudinal study of CVD. The Framingham Heart Study provides tremendous advantages for characterization of CVD outcomes and important risk factor information. The fact that ketchup was not listed as a standard item of the FFQ is a potential limitation of this study. Although participants could chose to include ketchup as an additional food item, it is likely that many participants did not report ketchup consumption. Ketchup is a concentrated source of lycopene that contains approximately the same amount of lycopene per weight as tomato sauce[37]. However, because of its small serving size relative to other important lycopene food sources (typically <15% by weight), the contribution of lycopene per serving is relatively small, so the misclassification of lycopene intake based on the incomplete ascertainment of ketchup intake should be modest overall, although it could be substantial for individuals who frequently consume ketchup. The FFQ also did not capture

lycopene from single nutrient supplements, although we were able to measure lycopene included in multivitamins. As with ketchup, the average contribution from lycopene supplements would likely be small in this population but we would substantially misclassify lycopene intake for anyone who used these supplements. However, the misclassification associated with both ketchup and lycopene supplements would tend to weaken any observed association between lycopene and tomato intake and CVD risk. Finally, we did not adjust for overall vegetable and fruit intake because these are the dietary sources of lycopene and adjusting for all fruits and vegetables (including those that contribute to lycopene intake) may result in some degree of over-adjustment. Instead we chose to adjust for various bioactive compounds found in vegetables and fruits that may have the potential to confound the relation between lycopene intake and CVD.

Evidence linking lycopene intake to intermediate CVD risk factors is somewhat limited in both experimental and human studies. *In vitro* and animal studies suggest that lycopene can inhibit production of reactive oxygen species, inflammation and platelet aggregation, reduce lipid peroxides, and decrease total and LDL cholesterol levels[38]. A meta-analysis of small human intervention studies reported that lycopene intakes of approximately 25 mg/d resulted in a 10% reduction in LDL cholesterol relative to subjects on lycopene-free diets and a small number of interventions of between 4.5 and 15 mg/d of lycopene resulted in a significant 5 mmHg drop in systolic blood pressure[39]. A recent observational study was also able to demonstrate an inverse association between tomato product consumption and cholesterol concentrations[40]. Serum LDL conjugated dienes, a marker of lipid oxidation, was also related to plasma lycopene in women but not men[41].

Our study of lycopene and incident CVD adds to the accumulating evidence that lycopene is related to CVD risk. However, tomatoes and tomato-based products are by far the most important dietary sources of lycopene in observational studies and most human lycopene trials are performed using tomato-based interventions. Thus, it is difficult to separate out the potential lycopene contribution to cardiovascular health from the overall contribution from tomato products and their other components. For example, tomatoes have been identified as a source of 9-oxo-10,12-octadecadienoic acid and its isomers, which are important oxylipins synthesized in plants that may act as peroxisome proliferator-activated receptor-α (PPARα) agonists affecting lipid metabolism[42]. Tomatoes have also been identified as a source of natural salicylates (3.1 μg/100 g), although it is not known if the dietary levels of salicylates provided by tomato products would be sufficient to produce any cardiovascular benefits[43]. Additional research is needed to sort out the potential benefits of tomatoes and their phytochemical components on CVD risk.

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Table 1

Lycopene and tomato product intake and incidence of cardiovascular disease (CVD), coronary heart disease (CHD) and stroke estimated from hazard ratio (HR) among adult men and women from the Framingham Offspring Cohort*

	CVD			CHD			Stroke		
	# events	HR (95%CI)	p-value	# events	HR (95% CI)	p-value	# events	HR (95% CI)	p-value
Lycopene Intake†									
Exam 5 & 6 Average‡		23,573 person-years			23,618 person-years			23,609 person-years	
Model 1§	314	0.92 (0.77, 1.10)//	0.39	171	0.77 (0.61, 0.96)	0.03	99	1.05 (0.76, 1.46)	0.76
Model 2¶	314	0.87 (0.72, 1.05)	0.16	171	0.76 (0.60, 0.97)	0.03	99	1.08 (0.75, 1.55)	0.68
Model 3**	314	0.86 (0.71, 1.05)	0.13	171	0.74 (0.58, 0.94)	0.01	99	1.07 (0.74, 1.54)	0.74
Exam 5, 6 and 7 Average††		15,858 person-years			15,870 person-years			15,880 person-years	
Model 1	219	0.87 (0.73, 1.04)	0.14	115	0.86 (0.68,1.08)	0.20	66	0.92 (0.65, 1.32)	0.67
Model 2	219	0.82 (0.70, 0.97)	0.03	115	0.84 (0.68, 1.05)	0.13	66	0.83 (0.58, 1.18)	0.31
Model 3	219	0.83 (0.70, 0.98)	0.03	115	0.84 (0.67, 1.03)	0.10	66	0.82 (0.59, 1.16)	0.27
Tomato Product Consumption‡‡									
Exam 5 & 6 Average		23,573 person-years			23,618 person-years			23,609 person-years	
Model 1	314	0.98 (0.94, 1.02)§§	0.45	171	0.94 (0.88, 0.99)	0.04	99	1.02 (0.95, 1.08)	0.63
Model 2	314	0.98 (0.94, 1.02)	0.28	171	0.94 (0.88,1.00)	0.05	99	1.02 (0.96, 1.09)	0.51
Model 3	314	0.97 (0.93, 1.02)	0.24	171	0.92 (0.86,0.99)	0.02	99	1.02 (0.96, 1.10)	0.51
Exam 5, 6 and 7 Average		15,858 person-years			15, 870 person-years			15,880 person-years	
Model 1	219	0.97 (0.916, 1.022)	0.25	115	0.95 (0.87, 1.02)	0.16	66	1.02 (0.93, 1.11)	0.68
Model 2	219	0.94 (0.887, 0.999)	0.05	115	0.93 (0.85, 1.001)	0.08	66	1.00 (0.91, 1.10)	0.99
Model 3	219	0.94 (0.878, 0.995)	0.03	115	0.90 (0.83, 0.99)	0.03	66	0.99 (0.90, 1.10)	0.91

*At the 5th study examination, the Framingham Offspring cohort participants had a mean age of 54 years (range 26-79 years) and a mean BMI of 27.2 kg/m^2 (range 14-54 kg/m^2). Fifty-six percent of the participants were women, 18% were current smokers, and 16% and 5% had a history of hypertension and diabetes, respectively.

†Mean lycopene intake was 7.6, 7.9 and 8.0 mg/d at the 5th, 6th and 7th examinations, respectively.

‡Intake is the average of intakes assessed at the Framingham Offspring cohort 5th and 6th examinations and follow-up time is counted from the date of the 6th examination.

§Model 1: adjusted for age and sex.

‖Lycopene intake was transformed using a natural logarithm. Consequently, the hazards ratios are interpreted as the relative risk for a 2.7-fold difference (i.e., a 1 unit difference on the natural logarithm scale) in lycopene intake.

¶Model 2: adjusted for age, sex, systolic BP, total cholesterol, total cholesterol/HDL ratio, BMI, smoking, number of packs per day, hypertension treatment, diabetes, saturated fat intake and energy intake.

**Model 3: adjusted for variables in Model 2 plus β-carotene, flavonol, vitamin C and vitamin E intakes.

††Intake is the average of intakes assessed at the Framingham Offspring cohort 5^{th}, 6^{th} and 7^{th} examinations and follow-up time is counted from the date of the 7^{th} examination.

‡‡Mean consumption of tomatoes and tomato-based products was 4.4, 4.4 and 4.6 servings/wk at the 5^{th}, 6^{th} and 7^{th} examinations, respectively.

§§The hazard ratios reflect the relative risk for one serving per day difference in tomato product consumption.