

## The Consumption of Lycopene and Tomato-Based Food Products Is Not Associated with the Risk of Type 2 Diabetes in Women<sup>1</sup>

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**ABSTRACT** Lycopene is a major carotenoid with potent antioxidant properties that may provide protection against the development of type 2 diabetes mellitus (DM). In this study we examined the association between baseline dietary intakes of lycopene, lycopene-containing foods, and the subsequent development of type 2 DM in a large prospective cohort study. We analyzed a total of 35,783 women from the United States, aged  $\geq 45$  y and free from self-reported cardiovascular disease, cancer, and DM at baseline. Intakes of lycopene and total and individual tomato-based food products were assessed by a 131-item-validated semiquantitative food-frequency questionnaire. During a median follow-up of 10.2 y, 1544 cases of incident type 2 DM were documented. After adjusting for age, total energy intake, randomized treatment assignment, body mass index, and other known DM risk factors, the multivariate-adjusted relative risks and 95% CI of type 2 DM across increasing quintiles of dietary lycopene, were 1.00 (baseline), 1.10 (0.94–1.29), 1.10 (0.94–1.29), and 1.07 (0.91–1.26) ( $P$  linear trend = 0.56). Compared with women who consumed  $< 1.5$  servings/wk total tomato-based food products, women who consumed 1.5 to  $< 4$ , 4 to  $< 7$ , 7 to  $< 10$ , and  $\geq 10$  servings/wk had multivariate relative risks (95% CI) of 1.03 (0.88–1.20), 1.02 (0.87–1.20), 1.09 (0.89–1.33), and 1.04 (0.80–1.36), respectively ( $P$  linear trend = 0.54). The associations for individual tomato-based food products were similar to the results for the combination of all tomato products. Our study found little evidence for an association between dietary intake of lycopene or lycopene-containing foods and the risk of type 2 DM. *J. Nutr.* 136: 620–625, 2006.

**KEY WORDS:** • lycopene • tomato products • intake • diabetes mellitus • epidemiology

Oxidative stress is implicated in the pathogenesis of type 2 diabetes mellitus (DM)<sup>3</sup> by inducing insulin resistance in the peripheral tissues and impairing insulin secretion from pancreatic  $\beta$ -cells (1–3). The abundant conjugated double bonds of carotenoids can scavenge peroxy radicals, making them powerful antioxidants that may provide protection against the development of type 2 DM. Lycopene, a carotenoid without provitamin A activity, is one of the major carotenoids detected in human tissues. Compared with other carotenoids, lycopene in vitro has been shown to have more potent antioxidant properties (4). Dietary intake of lycopene predominantly comes from the consumption of tomatoes or tomato products such as tomato juice, tomato sauce, and ketchup (5).

Epidemiologic studies that assess the role of lycopene in the primary prevention of type 2 DM are limited. There is indirect

evidence for a protective effect that has been indicated in previous cross-sectional studies (6–12). However, the only known prospective study on dietary lycopene and the risk of type 2 DM did not find significant associations in a Finnish cohort of men and women (13). We therefore sought to examine the association between baseline dietary intake of lycopene and subsequent development of type 2 DM in a large cohort of middle-aged and older women from the United States. We also investigated whether the dietary intakes of combined or individual lycopene-containing foods were associated with the risk of type 2 DM.

### SUBJECTS AND METHODS

**Study population.** The Women's Health Study (WHS) was a randomized, double-blind, placebo-controlled clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease (CVD) and cancer (14), with the  $\beta$ -carotene component terminated after a median treatment duration of 2.1 y (15). In 1992, a total of 39,876 female United States health professionals, aged  $\geq 45$  y, 94% Caucasian, and free from self-reported CVD and cancer (except nonmelanoma skin cancer), were randomized into the WHS. Among them, 39,310 women provided detailed dietary information at baseline

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<sup>3</sup> Abbreviations used: CVD, cardiovascular disease; DM, diabetes mellitus; RR, relative risk; SFFQ, semiquantitative food frequency questionnaire; WHS, Women's Health Study.

by completing a 131-item validated semiquantitative food frequency questionnaire (SFFQ) (16). Of the 39,310 women, 829 were excluded from the present analysis due to insufficient completion of the questionnaire (>70 items left blank) or an implausible mean energy intake of either <600 or  $\geq 3500$  kcal/d (1 kcal = 4.1888 kJ). Women with incomplete data on consumption of tomato-based food products ( $n = 1784$ ), prevalence of DM ( $n = 1160$ ), or prerandomization CVD or cancer ( $n = 37$ ) were also excluded. A final sample of 35,783 women remained for analysis. The study protocol was approved by Brigham and Women's Hospital Institutional Review Board.

**Lycopene, lycopene food sources, and other baseline covariates.** For each food item, a commonly used unit or portion size was specified on the SFFQ. Participants were asked how often they had consumed that amount, on average, during the previous year. Nine possible responses ranging from "never or less than once per month" to "6+ per day" were recorded. The average daily intakes for the individual food items were calculated by multiplying the intake frequency by the portion size. Four tomato-based food products specifically included on the SFFQ (tomatoes, tomato juice, tomato sauce, and pizza) were considered major lycopene food sources. The total intake of tomato-based foods was computed by adding the intakes of the 4 tomato-based food products. Nutrient intakes were computed by multiplying the intake frequency of each unit of food by the nutrient content of the specified portion size according to food composition tables from the Harvard School of Public Health (17). Each nutrient reported was adjusted for total energy intake using the residual method (18). The SFFQ used in the WHS has demonstrated reasonable validity as a measurement for long-term average dietary intakes in populations of health professionals (19). Previous validation studies have reported high correlations between the SFFQ and dietary records for lycopene food sources ( $r > 0.70$ ) (20,21).

On the baseline questionnaire, women provided self-reports of age (y), weight and height (calculated as BMI,  $\text{kg}/\text{m}^2$ ), smoking status (never, former, and current), alcohol use (rarely/never, 1–3 drinks/mo, 1–6 drinks/wk, and  $\geq 1$  drink/d), vigorous exercise (rarely/never, <1, 1–3, and  $\geq 4$  times/wk), family history of DM in a first-degree relative (no, yes), menopausal status (no, yes, and uncertain), postmenopausal hormone use (never, former, and current), and multivitamin use (never, former, and current). Also included were physician-diagnosed hypertension (no, yes), self-reported systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or any past or current treatment for high blood pressure. Measures for cholesterol included physician-diagnosed hypercholesterolemia (no, yes), self-reported cholesterol level  $\geq 240$  mg/dL (6.21 mmol/L), and any past or current treatment for high cholesterol.

**Ascertaining type 2 DM.** During annual follow-ups, participants were asked whether and when they had been diagnosed with DM since completing the last questionnaire. As described previously (22), two complementary approaches were used to confirm self-reported type 2 DM in the WHS. First, we attempted to contact 473 women with self-reported DM who provided a blood sample. Using the American Diabetes Association's diagnostic criteria (23), the self-reported diagnosis for type 2 DM was confirmed in 406 (91%) of 446 women who responded by telephone interview. Second, a random sample of 147 women with self-reported DM were sent a supplemental diabetes questionnaire. Among 136 respondents, 124 women (91%) were classified as having type 2 DM by the supplemental questionnaire. In addition, 113 of the 124 women gave us permission to contact their primary care physician. Of 113 physicians, 97 responded, and 90 of those provided adequate information for the American Diabetes Association's diagnostic criteria. Out of these 90 women, 89 (99%) were confirmed to have type 2 DM on the basis of combined information from the supplemental questionnaire and information from the physicians. This concluded our criteria for affirming the validity of self-reported type 2 DM in the WHS.

**Statistical analyses.** Statistical analysis was performed using SAS software, version 8 (SAS Institute). Univariate distributions were presented as means  $\pm$  SD for continuous variables and as proportional percentages for categorical variables. DM risk factors were first compared according to quintiles of lycopene intake. After testing the proportional hazard assumption, Cox regression models were used to estimate the relative risk (RR) and 95% CI of developing type 2 DM

across lycopene quintiles with the lowest quintile as the baseline category. Models were adjusted for age, total energy intake, and randomized treatment assignment, and then by lifestyle factors, including smoking, alcohol use, exercise, menopausal status, postmenopausal hormone use, multivitamin use, and family history of DM. They were also adjusted for clinical factors, including BMI, history of hypertension, and hypercholesterolemia; and finally, they were adjusted for other nutrient intake, including total fat, fiber, and dietary glycemic load. Major food sources of lycopene were categorized a priori. The intake of tomatoes (1 tomato = 1 serving) included 4 categories (none, 1–3 servings/mo, 1–4 servings/wk, and  $\geq 5$  servings/wk). The intake of tomato juice (small glass = 1 serving), tomato sauce (1/2 cup or 118 mL = 1 serving), and pizza (2 slices = 1 serving) were also divided into 4 categories (none, 1–3 servings/mo, 1 serving/wk, and  $\geq 2$  servings/wk). The total tomato-based food-product intake was divided into < 1.5, 1.5 to < 4, 4 to < 7, 7 to < 10, and  $\geq 10$  servings/wk as done in a previous study (24). Linear trends were tested using the median value of each intake category as an ordinal variable. We also tested curvilinear trends by modeling intake as a continuous variable with a quadratic term. Because the effect of lycopene on the risk of type 2 DM may be modified by existing insulin insensitivity, we also stratified the analysis by using surrogate markers of insulin sensitivity such as BMI (< or  $\geq 30$   $\text{kg}/\text{m}^2$ ), history of hypertension, and hypercholesterolemia (with or without). Interactions were tested using the Wald chi-square test, with  $P < 0.05$  considered statistically significant.

## RESULTS

The energy-adjusted lycopene intake was  $9241 \pm 6396$   $\mu\text{g}/\text{d}$  in 35,783 women aged  $54.5 \pm 7.0$  y. Women consuming greater amounts of lycopene tended to have a healthier lifestyle (Table 1). Compared with those in the lowest quintile of lycopene intake, women in higher quintiles were younger, had lower BMIs, were less likely to be current smokers, were more likely to exercise, drink alcohol moderately, and use postmenopausal hormones. Higher lycopene intake was also associated with a healthier diet pattern, including lower total-energy intake, energy-adjusted total-fat intake and dietary glycemic load, and a higher intake of fiber. As expected, increased lycopene intake paralleled a progressively higher intake of most tomato-based food products except pizza. The baseline self-reported history for the prevalence of hypertension and hypercholesterolemia were roughly comparable across quintiles of lycopene intake.

There were 1544 incident cases of type 2 DM during a median follow-up of 10.2 y (maximum of 10.9 y). Compared with women in the lowest quintile of dietary lycopene, the age-, energy intake-, and randomized treatment-adjusted RRs, and 95% CIs of type 2 DM across increasing quintiles were 0.93 (0.79–1.09), 0.96 (0.82–1.12), 0.97 (0.83–1.13), and 0.98 (0.83–1.14) ( $P$  linear trend = 0.96,  $P$  curvilinear trend = 0.11) (Table 2). Further adjustment for other lifestyle and clinical risk factors for type 2 DM did not reveal a significant association between lycopene intake and risk of type 2 DM. The addition of nutrient factors into the model did not materially modify the RRs (data not shown). Women with a lycopene intake at or above the 95th percentile, or  $\geq 20,482$   $\mu\text{g}/\text{d}$ , had a multivariate RR (95% CI) of 1.03 (0.78–1.35) vs. those in the lowest quintile after controlling for lifestyle and clinical factors.

On average, women consumed a total of  $4.33 \pm 3.22$  servings of tomato-based food products per week, of which 2.18 were from tomatoes, 1.14 from tomato sauce, 0.57 from pizza, and 0.44 from tomato juice. Women who consumed increasing amounts of tomato-based food products had neither significantly decreased nor increased risk of type 2 DM. Compared

TABLE 1

Baseline characteristics of 35,783 women according to quintiles of dietary lycopene intake<sup>1</sup>

Characteristics	Quintiles of lycopene intake <sup>2,3</sup>					P <sup>4</sup>
	1st	2nd	3rd	4th	5th	
Age, y	54.7 ± 7.2	54.2 ± 6.9	54.6 ± 7.0	54.5 ± 7.0	54.2 ± 6.8	<0.0001
BMI, kg/m <sup>2</sup>	26.1 ± 5.2	25.8 ± 4.8	25.9 ± 4.9	25.7 ± 4.8	25.8 ± 4.9	<0.0001
Smoking, %						<0.0001
Current	14.5	13.3	12.7	12.2	12.0	
Past	32.7	34.9	36.3	36.3	39.5	
Never	52.8	51.8	51.0	51.5	48.5	
Exercise, %						<0.0001
Rarely/never	44.0	39.4	36.6	35.9	33.7	
<1 time/wk	19.5	20.6	20.2	20.0	19.3	
1–3 times/wk	27.5	30.1	32.8	32.2	34.5	
≥4 times/wk	9.0	9.9	10.4	11.9	12.5	
Alcohol use, <sup>5</sup> %						<0.0001
Rarely/never	51.6	44.7	41.4	41.8	40.5	
1–3 drinks/mo	13.0	13.6	13.7	13.6	12.5	
1–6 drinks/wk	26.9	32.4	34.4	33.5	33.9	
≥1 drink/d	8.5	9.3	10.5	11.1	13.1	
Postmenopause, %	55.3	53.0	54.7	53.7	52.8	0.02
Postmenopausal hormone use, %						0.01
Current	40.6	41.4	42.8	42.9	43.3	
Past	10.4	9.7	9.6	10.4	10.0	
Never	49.0	48.9	47.6	46.7	46.7	
Multivitamin use, %						0.0002
Current	29.6	28.9	29.4	29.2	29.3	
Past	55.5	58.6	58.0	57.9	58.1	
Never	14.9	12.5	12.6	12.9	12.6	
History of hypertension, %	25.4	23.3	24.3	24.7	25.1	0.04
History of hypercholesterolemia, %	30.1	28.8	28.8	27.7	28.8	0.03
Family history of diabetes, %	26.0	23.3	25.4	24.7	24.5	0.003
Total energy intake, <sup>6</sup> kcal/d	1799 ± 537	1704 ± 505	1716 ± 556	1755 ± 543	1665 ± 512	<0.0001
Total fat, <sup>2</sup> g/d	59.6 ± 12.6	58.8 ± 11.6	57.8 ± 11.2	57.0 ± 11.3	55.1 ± 11.5	<0.0001
Glycemic load, <sup>2</sup> g/d	118 ± 23	117 ± 21	117 ± 20	117 ± 20	117 ± 21	0.008
Fiber, <sup>2</sup> g/d	17.0 ± 5.9	17.7 ± 5.4	18.8 ± 5.4	19.8 ± 5.5	21.5 ± 6.2	<0.0001
Combined tomato-based foods, <sup>7</sup> serving/wk	1.6 ± 0.8	2.6 ± 1.1	3.8 ± 1.5	5.3 ± 1.9	8.3 ± 4.1	<0.0001
Tomatoes, <sup>7</sup> serving/wk	0.6 ± 0.5	1.1 ± 0.9	2.0 ± 1.3	2.9 ± 1.7	4.3 ± 3.3	<0.0001
Tomato juice, <sup>7</sup> serving/wk	0.08 ± 0.2	0.2 ± 0.3	0.3 ± 0.4	0.5 ± 0.8	1.2 ± 2.2	<0.0001
Tomato sauce, <sup>7</sup> serving/wk	0.4 ± 0.3	0.7 ± 0.3	0.9 ± 0.6	1.4 ± 1.1	2.3 ± 1.7	<0.0001
Pizza, <sup>7</sup> serving/wk	0.5 ± 0.5	0.6 ± 0.6	0.6 ± 0.6	0.6 ± 0.6	0.6 ± 0.7	<0.0001

<sup>1</sup> Values are mean ± SD for continuous variables and proportion (%) for categorical variables.

<sup>2</sup> Energy adjusted using the residual method (18).

<sup>3</sup> 1st quintile:  $n = 7156$ , range ( $\mu\text{g/d}$ ) = <4501.7, median ( $\mu\text{g/d}$ ) = 3411; 2nd quintile:  $n = 7157$ , range ( $\mu\text{g/d}$ ) = 4501.8–<6530.4, median ( $\mu\text{g/d}$ ) = 5486; 3rd quintile:  $n = 7157$ , range ( $\mu\text{g/d}$ ) = 6530.5–<9141.2, median ( $\mu\text{g/d}$ ) = 7739; 4th quintile:  $n = 7157$ , range ( $\mu\text{g/d}$ ) = 9142–13093, median ( $\mu\text{g/d}$ ) = 10863; 5th quintile:  $n = 7156$ , range ( $\mu\text{g/d}$ ) = >13093, median ( $\mu\text{g/d}$ ) = 16755.

<sup>4</sup> P-values derived from ANOVA for continuous variables and chi-square test for categorical variables.

<sup>5</sup> One drink: 1 glass, bottle, or can for beer and light beer, 354.9 mL; a 4-oz. glass for red wine and white wine, 118.3 mL; or 1 drink or shot for liquor, 29.57 mL.

<sup>6</sup> To convert total energy intake from kcal/d to kJ/d, multiply by 4.1868.

<sup>7</sup> One serving: 1 tomato for tomatoes; 1 small glass for tomato juice; 1/2 cup or 118 mL for tomato sauce; and 2 slices for pizza.

with women consuming a total of <1.5 servings/wk of tomato products, the multivariate RR of type 2 DM were 1.03 (0.88–1.20), 1.02 (0.87–1.20), 1.09 (0.89–1.33), and 1.04 (0.80–1.36) for those consuming 1.5 to <4, 4 to <7, 7 to <10, and ≥10 servings/wk, respectively ( $P$  linear trend = 0.54,  $P$  curvilinear trend = 0.01). The results for more specific lycopene food sources were similar to the results for the total-tomato products. Women consuming intermediate amounts of tomatoes, tomato sauce, and pizza seemed to have a moderately lower risk of type 2 DM in the age-, energy-, and treatment-adjusted model, but these inverse associations were not statistically significant in the multivariate-adjusted models.

The analysis was then stratified by BMI (<30, ≥30 kg/m<sup>2</sup>), history of hypertension (no, yes), and history of hypercholes-

terolemia (no, yes). Subgroup results were similar to the overall results (data not shown), and the associations were not modified by BMI or history of hypertension or hypercholesterolemia (for all interactions  $P > 0.05$ ).

## DISCUSSION

In this large prospective cohort study of middle-aged and older women, we found no evidence for associations between either dietary lycopene or lycopene-containing foods and the risk of type 2 DM. This finding remained after adjusting for body weight and several risk factors for type 2 DM. The results suggest that dietary lycopene may not have a specific role in the primary prevention of type 2 DM.

TABLE 2

Relative risks and 95% confidence intervals of type 2 diabetes mellitus according to dietary intake of lycopene and lycopene food sources in 35,783 middle-aged and older women

	Categories of intakes					P <sup>1</sup> Linear trend	P <sup>2</sup> Curvilinear trend
	1st	2nd	3rd	4th	5th		
<b>Lycopene</b>							
Range, $\mu\text{g}/\text{d}^3$	<4501.7	4501.8–<6530.4	6530.5–<9141.2	9142–13093	>13093		
Cases/person-years <sup>4</sup>	328/70315	294/70463	307/70473	312/70237	303/70205		
Age, energy (treatment adjusted)	1.00 (reference)	0.93 (0.79–1.09)	0.96 (0.82–1.12)	0.97 (0.83–1.13)	0.98 (0.83–1.14)	0.96	0.11
Multivariate model 1 <sup>5</sup>	1.00 (reference)	1.03 (0.88–1.21)	1.09 (0.93–1.28)	1.10 (0.94–1.28)	1.14 (0.97–1.33)	0.10	0.73
Multivariate model 2 <sup>6</sup>	1.00 (reference)	1.10 (0.94–1.29)	1.10 (0.94–1.29)	1.11 (0.95–1.31)	1.07 (0.91–1.26)	0.56	0.43
<b>Combined tomato products<sup>7</sup></b>							
Range, servings/wk	<1.5	1.5–<4	4–<7	7–<10	$\geq 10$		
Cases/person-years	249/58147	554/130981	444/104940	212/42153	85/15472		
Age, energy (treatment adjusted)	1.00 (reference)	0.93 (0.80–1.08)	0.87 (0.74–1.02)	0.98 (0.81–1.19)	1.00 (0.77–1.30)	0.86	0.006
Multivariate model 1 <sup>5</sup>	1.00 (reference)	1.03 (0.88–1.19)	1.01 (0.86–1.19)	1.15 (0.95–1.40)	1.15 (0.88–1.49)	0.15	0.05
Multivariate model 2 <sup>6</sup>	1.00 (reference)	1.03 (0.88–1.20)	1.02 (0.87–1.20)	1.09 (0.89–1.33)	1.04 (0.80–1.36)	0.54	0.01
<b>Tomatoes<sup>7</sup></b>							
Range, servings/wk	None	1–3/month	1–4/wk	$\geq 5/\text{wk}$			
Cases/person-years	97/19212	286/72195	933/215987	228/44299			
Age, energy (treatment adjusted)	1.00 (reference)	0.77 (0.61–0.97)	0.78 (0.64–0.97)	0.86 (0.68–1.10)		0.87	0.17
Multivariate model 1 <sup>5</sup>	1.00 (reference)	0.81 (0.64–1.02)	0.90 (0.73–1.11)	0.99 (0.77–1.26)		0.13	0.74
Multivariate model 2 <sup>6</sup>	1.00 (reference)	0.81 (0.64–1.03)	0.94 (0.76–1.17)	0.95 (0.74–1.22)		0.19	0.36
<b>Tomato juice<sup>7</sup></b>							
Range, servings/wk	None	1–3/month	1/wk	$\geq 2/\text{wk}$			
Cases/person-years	904/212661	369/85275	175/33486	96/20271			
Age, energy (treatment adjusted)	1.00 (reference)	0.97 (0.86–1.10)	1.14 (0.97–1.34)	1.01 (0.82–1.25)		0.62	0.71
Multivariate model 1 <sup>5</sup>	1.00 (reference)	1.03 (0.91–1.17)	1.21 (1.02–1.42)	1.09 (0.88–1.36)		0.17	0.42
Multivariate model 2 <sup>6</sup>	1.00 (reference)	1.00 (0.88–1.13)	1.11 (0.94–1.31)	0.93 (0.74–1.15)		0.74	0.90
<b>Tomatoes sauce<sup>7</sup></b>							
Range, servings/wk	None	1–3/month	1/wk	$\geq 2/\text{wk}$			
Cases/person-years	160/33124	518/122094	569/132250	297/64225			
Age, energy (treatment adjusted)	1.00 (reference)	0.87 (0.73–1.04)	0.84 (0.70–1.00)	0.84 (0.68–1.02)		0.32	0.02
Multivariate model 1 <sup>5</sup>	1.00 (reference)	0.93 (0.78–1.11)	0.94 (0.78–1.12)	0.97 (0.79–1.18)		0.83	0.02
Multivariate model 2 <sup>6</sup>	1.00 (reference)	0.97 (0.81–1.17)	1.01 (0.84–1.21)	1.03 (0.84–1.26)		0.56	0.03
<b>Pizza<sup>7</sup></b>							
Range, servings/wk	None	1–3/month	1/wk	$\geq 2/\text{wk}$			
Cases/person-years	403/88018	695/166880	376/84690	70/12104			
Age, energy (treatment adjusted)	1.00 (reference)	0.89 (0.78–1.01)	0.92 (0.79–1.06)	1.08 (0.83–1.40)		0.68	0.62
Multivariate model 1 <sup>5</sup>	1.00 (reference)	0.92 (0.81–1.04)	0.95 (0.82–1.11)	1.05 (0.80–1.36)		0.74	0.79
Multivariate model 2 <sup>6</sup>	1.00 (reference)	0.90 (0.79–1.02)	0.94 (0.81–1.09)	0.97 (0.75–1.27)		0.90	0.65

<sup>1</sup> Linear trends were tested using the median value of each category as an ordinal variable.

<sup>2</sup> Curvilinear trends were tested by modeling dietary intake as continuous variable together with the quadratic term.

<sup>3</sup> Energy adjusted using the residual method (18).

<sup>4</sup> Person-years was the sum of follow-up time for women who developed hypertension (incident cases) and those who did not (noncases). Follow-up time was calculated as the time from randomization to the diagnosis date of type 2 DM for incident cases and the time from randomization to the last day known in the follow-up of study for noncases.

<sup>5</sup> Multivariate model 1: additionally adjusted for smoking (never, former, current), alcohol use (rarely/never, 1–3 drinks/mo, 1–6 drinks/wk,  $\geq 1$  drink/d), exercise (rarely/never, <1, 1–3,  $\geq 4$  times/wk), family history of diabetes (no, yes), postmenopause (no, yes, uncertain), postmenopausal hormone use (never, former, current), multivitamin use (never, former, current).

<sup>6</sup> Multivariate model 2: multivariate model 1 plus BMI (continuous), history of hypertension (yes, no), history of hypercholesterolemia (no, yes).

<sup>7</sup> One serving: 1 tomato for tomatoes; 1 small glass for tomato juice; 1/2 cup or 118 mL for tomato sauce; and 2 slices for pizza.

Protection against oxidative damage is theorized to be the biological link between lycopene and the metabolism of glucose. Increased free radical activities impair insulin action and glucose disposal in the peripheral tissues (2,3,25,26). Free radical-mediated tissue damage also contributes to  $\beta$ -cell dysfunction (1,3,26–28). Furthermore, evidence is accumulating that oxidative stress may be actively involved in the

pathogenesis of chronic inflammation, a possible common pathway underlying insulin resistance, type 2 DM, and CVD (3). An in vitro study demonstrated that lycopene has the strongest single oxygen-quenching capacity among the major antioxidant carotenoids (4), which may play a protective role in preventing diseases associated with free radical attack, including type 2 DM. Several human intervention studies have shown

improvements in LDL oxidation by lycopene-containing foods or lycopene supplementation (29–31). However, direct evidence regarding the beneficial effect of lycopene on insulin action and glucose tolerance is still lacking. One animal study found that feeding a natural tomato extract containing 5% lycopene had no significant effect on plasma glucose levels in diabetic rats (32). Similarly, a randomized trial of 57 patients with well-controlled type 2 DM reported that short-term dietary supplementation with tomato juice, 250 mL twice daily for 4 wk, increased plasma lycopene and LDL resistance to oxidation, but did not change plasma glucose (33). Our prospective study of middle-aged and older women did not provide additional support for the potential benefits of long-term high lycopene intake in preventing the development of type 2 DM.

Previous epidemiologic studies on the relation between lycopene intake and risk of type 2 DM are scarce. In a cross-sectional study (7), food records suggested that a greater dietary lycopene intake was associated with reduced fasting plasma glucose concentration in nondiabetic male, but not female, relatives of patients with type 2 DM. Plasma concentrations of lycopene have been shown to have an inverse association with type 2 DM, fasting blood glucose, glucose tolerance, or glycosylated hemoglobin in population-based surveys (6,8) and cross-sectional analyses (9–12). However, these cross-sectional observations cannot directly infer any cause-effect relation. The low concentration of serum lycopene observed in patients with DM or impaired glucose metabolism may reflect a depleted antioxidant system due to DM or a change in diet after diagnosis. To our knowledge, there is only 1 published study that examines the prospective association between dietary lycopene and incidence of type 2 DM (13). In this Finnish cohort of 2285 men and 2019 women, aged 40–69 y and free of type 2 DM and heart disease at baseline, no associations were found between baseline lycopene intake (estimated using a dietary history interview) and the risk of type 2 DM during 23-y of follow-up. The results of our study of middle-aged and older U.S. women corroborate this earlier finding. Our study also shows no association between the combined or individual lycopene-containing foods and the risk of type 2 DM.

The correlation between dietary and plasma lycopene in a subsample of 483 women in WHS was statistically significant but weak (age-adjusted Spearman rank correlation coefficient  $r = 0.14$ ) (24). This may reflect a large interindividual variation in blood lycopene in response to dietary intake. Heating, processing, and the simultaneous ingestion of fat have been seen to improve the bioavailability of lycopene, but the specific biological mechanisms underlying lycopene absorption and in vivo metabolism remain poorly understood (34).

The prospective design, long period of follow-up, validated diet assessment, and documentation of a large number of incident type 2 DM cases are the unique strengths of our study. Yet several methodological issues must be considered as potential limitations. First, the single measurement of dietary intake at baseline and lack of cohort-wide screening in identifying undiagnosed DM may induce nondifferential misclassification and therefore bias the association toward null. Second, high lycopene intake may simply coincide with other lifestyle or dietary patterns that may be associated with glucose metabolism. Although we comprehensively adjusted for multiple DM risk factors in our analysis, residual confounding may remain. Third, these findings might be restricted to middle-aged and older, mostly nonhispanic, white women who were generally healthy and willing to participate in a clinical trial. Lycopene intake in our study was

comparable to other published large U.S. cohort studies; however, further research is necessary to consider lycopene intake in a variety of populations and conditions and to assess its association with the risk of type 2 DM.

In conclusion, our study found little evidence for an association between dietary intake of lycopene or lycopene-containing foods and the risk of type 2 DM. More research is needed to further elucidate the biological mechanisms of lycopene absorption and metabolism and to determine the specific role of lycopene in the development of type 2 DM.

## LITERATURE CITED

1. Oberley LW. Free radicals and diabetes. *Free Radic Biol Med.* 1988; 5:113–24.
2. Paolisso G, Giugliano D. Oxidative stress and insulin action: is there a relationship? *Diabetologia.* 1996;39:357–63.
3. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol.* 2004;24:816–23.
4. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys.* 1989;274: 532–8.
5. Clinton SK. Lycopene: chemistry, biology, and implications for human health and disease. *Nutr Rev.* 1998;56:35–51.
6. Bates CJ, Lean ME, Mansoor MA, Prentice A. Nutrient intakes; biochemical and risk indices associated with Type 2 diabetes and glycosylated haemoglobin, in the British National Diet and Nutrition Survey of people aged 65 years and over. *Diabet Med.* 2004;21:677–84.
7. Ylonen K, Alfthan G, Groop L, Saloranta C, Aro A, Virtanen SM. Dietary intakes and plasma concentrations of carotenoids and tocopherols in relation to glucose metabolism in subjects at high risk of type 2 diabetes: the Botnia Dietary Study. *Am J Clin Nutr.* 2003;77:1434–41.
8. Ford ES, Will JC, Bowman BA, Narayan KM. Diabetes mellitus and serum carotenoids: findings from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 1999;149:168–76.
9. Armstrong AM, Chestnutt JE, Gormley MJ, Young IS. The effect of dietary treatment on lipid peroxidation and antioxidant status in newly diagnosed noninsulin dependent diabetes. *Free Radic Biol Med.* 1996;21:719–26.
10. Polidori MC, Mecocci P, Stahl W, Parente B, Cecchetti R, Cherubini A, Cao P, Sies H, Senin U. Plasma levels of lipophilic antioxidants in very old patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2000;16:15–9.
11. Suzuki K, Ito Y, Nakamura S, Ochiai J, Aoki K. Relationship between serum carotenoids and hyperglycemia: a population-based cross-sectional study. *J Epidemiol.* 2002;12:357–66.
12. Chuang CZ, Subramaniam PN, LeGardeur BY, Lopez A. Risk factors for coronary artery disease and levels of lipoprotein(a) and fat-soluble antioxidant vitamins in Asian Indians of USA. *Indian Heart J.* 1998;50:285–91.
13. Montonen J, Knekt P, Jarvinen R, Reunanen A. Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care.* 2004;27:362–6.
14. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. *Journal of Myocardial Ischemia.* 1992;4:27–9.
15. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst.* 1999;91:2102–6.
16. Liu S, Manson JE, Lee IM, Cole SR, Hennekens CH, Willett WC, Buring JE. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr.* 2000;72:922–8.
17. Watt B, Merrill A. Composition of foods: raw, processed, prepared, 1963–1992: Agriculture handbook no. 8. Washington, DC: U.S. Department of Agriculture, U.S. Government Printing Office; 1993.
18. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986;124:17–27.
19. Willett WC. *Nutritional epidemiology.* 2nd ed. New York: Oxford University Press; 1998.
20. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc.* 1993;93: 790–6.
21. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol.* 1989;18:858–67.
22. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. *Diabetes Care.* 2004;27:2108–15.
23. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183–97.
24. Sesso HD, Liu S, Gaziano JM, Buring JE. Dietary lycopene, tomato-based food products and cardiovascular disease in women. *J Nutr.* 2003;133: 2336–41.

25. Paolisso G, D'Amore A, Di Maro G, Galzerano D, Tesauro P, Varricchio M, D'Onofrio F. Evidence for a relationship between free radicals and insulin action in the elderly. *Metabolism*. 1993;42:659-63.
26. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? *Diabetes*. 2003;52:1-8.
27. Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes*. 2003;52:581-7.
28. Sakai K, Matsumoto K, Nishikawa T, Suefuji M, Nakamaru K, Hirashima Y, Kawashima J, Shirotani T, Ichinose K, et al. Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells. *Biochem Biophys Res Commun*. 2003;300:216-22.
29. Agarwal S, Rao AV. Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. *Lipids*. 1998;33:981-4.
30. Bub A, Watzl B, Abrahamse L, Delincee H, Adam S, Wever J, Muller H, Rechkemmer G. Moderate intervention with carotenoid-rich vegetable products reduces lipid peroxidation in men. *J Nutr*. 2000;130:2200-6.
31. Steinberg FM, Chait A. Antioxidant vitamin supplementation and lipid peroxidation in smokers. *Am J Clin Nutr*. 1998;68:319-27.
32. Pollack A, Oren P, Stark AH, Eisner Z, Nyska A, Madar Z. Cataract development in sand and galactosemic rats fed a natural tomato extract. *J Agric Food Chem*. 1999;47:5122-6.
33. Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care*. 2000;23:733-8.
34. Shi J, Le Maguer M. Lycopene in tomatoes: chemical and physical properties affected by food processing. *Crit Rev Food Sci Nutr*. 2000;40:1-42.