NUTRITION AND CANCER, *36*(2), 163–169

Correlates of Serum Lycopene in Older Women

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Abstract: *Experimental and epidemiological evidence suggests that lycopene, a predominant carotenoid found in human serum, may reduce the risk of certain cancers. We examined the association of dietary, physiological, and other factors with serum lycopene concentrations in a subsample of 946 postmenopausal women participating in the Women's Health Initiative. Pearson partial correlation coefficients and linear regression coefficients were calculated after adjustment for age, ethnicity, and serum low-density-lipoprotein (LDL) cholesterol. Serum lycopene was correlated with serum LDL cholesterol (*$r = 0.23$*) and dietary lycopene (*$r = 0.17$*, both* $p < 0.001$*). Individual food items found to be correlated with serum lycopene after adjustment included fresh tomatoes or tomato juice (*$r = 0.11$*), cooked tomatoes, tomato sauce, or salsa (*$r = 0.17$*), and spaghetti with meat sauce (*$r = 0.19$*, all* $p < 0.01$*). Age and body mass index were negatively associated with serum lycopene levels (both* $p < 0.001$*). Serum lycopene levels were highest in the summer and highest for those living in the northeastern United States. If we postulate that high serum lycopene levels reduce cancer risk, it becomes apparent that we have limited ability to detect this association from studies of lycopene intake. An understanding of factors associated with serum lycopene levels can be useful for the interpretation of studies of dietary lycopene and disease risk.*

Introduction

Over the past decade, considerable research has focused on the role of the carotenoids in cancer prevention. However, among the approximately 40 known dietary carotenoids, only β-carotene has been studied extensively. There is increasing evidence that lycopene may play an important role in cancer prevention (1). Lycopene may be particularly important, because it comprises roughly one-half the total carotenoid concentration of human serum in American populations and has the greatest ability of all the common carotenoids to quench singlet oxygen, thus protecting against oxidative damage (2). In cell cultures, lycopene is a more effective inhibitor of human endometrial, mammary, and lung cancer cell proliferation than α- or β-carotene (3). Also, a number of epidemiological studies have found associations of lycopene consumption with a decreased risk of prostate cancer (4,5), cervical intraepithelial neoplasia (6), stomach cancer (7), and pancreatic cancer (8).

Although most carotenoids are distributed in a wide array of fruits and vegetables, lycopene is contained in relatively few foods. Over 85% of dietary lycopene is obtained from tomatoes and tomato products such as tomato juice, tomato paste and sauce, ketchup, and raw tomatoes (9,10). The lycopene content of tomatoes and tomato products varies widely, up to threefold, by the variety of tomato and degree of ripeness, and heating lycopene-rich foods with fat appears to increase its bioavailability (9,11). Less-concentrated sources of lycopene include pink grapefruit, guava, watermelon, and papaya.

Blood levels of lycopene are influenced by dietary intake but are less influenced by day-to-day variation in intake than other carotenoids (12). For example, one study found that the plasma depletion half-life of lycopene was between 12 and 33 days, in comparison to a <12-day half-life for β-carotene (13). There is limited information concerning other determinants of serum lycopene. Unlike other carotenoids, lycopene levels do not appear to be higher in women than in men and appear to decrease with age (14). Data are conflicting regarding the relationship of serum lycopene levels to cigarette smoking (14–18), a major source of oxidative stress, and alcohol consumption (14,19,20).

The objective of this study was to identify factors associated with serum lycopene in a sample of ethnically diverse older women. Specifically, we examined the association of serum lycopene with 1) lycopene intake, lycopene-rich foods, and other dietary factors, 2) serum lipids and other carotenoids, and 3) sociodemographic factors and health behavior. An understanding of determinants of a biochemical

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measure, such as serum lycopene, can provide valuable information for epidemiological studies on lycopene intake and cancer risk.

Methods

Study Population

Participants in this study were a subsample drawn from the Women's Health Initiative (WHI) Clinical Trials of dietary modification and hormone replacement therapy. Study participants were enrolled at 40 participating clinical centers throughout the United States. Inclusion in the clinical trials required that women be postmenopausal and between 50 and 79 years of age. A detailed description of the WHI study has been published (21).

Sample Selection

Six percent of women enrolled in the clinical trial components of the WHI were randomly selected to have their blood analyzed for lipids and blood nutrients. The random sampling procedure was stratified by clinical center, age, hysterectomy status, and ethnic status to oversample minority women. Women included in this analysis were randomized into the WHI clinical trial between 13 January 1994 and 2 October 1996, and blood was analyzed by 12 May 1998 (n = 1,050). For two women, the analysis of lycopene failed because of an insufficient serum sample. Participants with food frequency questionnaire (FFQ) energy estimates of <600 kcal (n = 21) or ≥3,500 kcal (n = 36) were excluded from the analysis, because these energy estimates suggest that the FFQ was not completed in a reasonable manner. Thirty-four respondents enrolled in the Honolulu Clinical Center were excluded because they completed a version of the FFQ modified for Asian-Pacific eating patterns, and therefore their dietary intake estimates may not be entirely comparable to those in the main study. An additional 11 participants had missing FFQ data, leaving a final sample of 946 participants.

Data Collection

The analyses were based on information collected at baseline. The WHI baseline protocol entailed mailed self-administered questionnaires, telephone-administered questionnaires, and three clinic visits. Clinic visits included interviewer-administered questionnaires, physical measurements (e.g., height and weight), and a fasting blood draw.

Demographic and behavioral variables were based on self-report. Demographic factors included race, ethnicity, education, income, age, and marital status. Health behaviors included cigarette smoking, alcohol consumption, and physical activity. We estimated alcohol consumption from the FFQ, summing across frequency (and portion sizes) of beer, wine, and liquor intake. Recreational physical activity was assessed by questions on the frequency and duration of four speeds of walking and of three other types of recreational activity classified as light, moderate, or strenuous. We calculated weekly episodes of moderate or strenuous activity, where moderate or strenuous activity was defined as ≥4.0 metabolic equivalents ($kcal \cdot wk^{-1} \cdot kg^{-1}$) (22).

Dietary intake was assessed from a semiquantitative FFQ based on the instrument used in the Women's Health Trial Feasibility Study in Minority Populations (23). Details of the measurement characteristics of this FFQ have been published (24). The FFQ is divided into three sections: adjustment questions, food line items, and summary questions. The adjustment questions are used to modify the means by which the analysis software derives the nutrient content of certain foods by inquiring about food preparation practices, added fats, and fiber intake. The food line item section includes questions about the frequency of consumption over the last three months and portion size of 122 foods or food groups. Intake of individual foods was obtained by multiplying the frequency of consumption of each food by the portion size. The summary questions cover four topics: usual intake of fruits, usual intake of vegetables, types of fat added to foods, and types of fat used in cooking. Summary questions are used to adjust total fruit and vegetable intake derived from responses to the food line items. FFQ nutrients were calculated using a database derived from the University of Minnesota Nutrition Coding Center that was modified using updated values of lycopene content in specific foods (25,26). We calculated servings of fruits and vegetables per day using the sum of servings of fruit juices, potatoes, and salads and the summary questions on fruits and vegetables.

Information on the use of vitamin supplements was ascertained by an interviewer-administered computer-driven inventory of all nutritional supplements taken by the participant. Supplemental intake of nutrients included intake from multivitamin supplements as well as individual supplements. Details of the supplement inventory procedure have been published elsewhere (27).

Twelve-hour fasting blood samples were collected at a baseline clinic visit. Blood was processed at each clinical center, centrifuged and aliquoted, and frozen to −70°C for forwarding to the central storage facility (McKesson BioServices). The time from blood draw to freezing averaged 80 minutes. Blood samples chosen for analyses were shipped to Medical Research Laboratories in Highland Heights, KY, for analysis. The carotenoids were analyzed using a high-performance liquid chromatography method based on a modification of the procedures of Kaplan and co-workers (28). Cholesterol was analyzed using a cholesterol oxidase method (29). Triglyceride was analyzed by an enzymatic method with a glycerol blank (30). Quality control procedures consisted of analyses of aliquots of quality control pools and blind duplicates with each batch of blood samples and the analysis of round robin samples from the National Institute of Standards and Technology Micronutrients Quality Assurance Program.

The average number of days from the completion of the FFQ to the blood draw and vitamin supplement inventory was 35.

Statistical Analyses

The dependent variable of interest was serum lycopene. Although the distribution was skewed to the right, logarithmic transformation did not improve normality, and therefore serum lycopene was not logarithmically transformed in any of the analyses.

Three types of independent variables were examined: 1) serum measures, 2) dietary measures including vitamin supplements, and 3) participant characteristics such as sociodemographics, health behavior, geographic region of residence, and season of blood draw. Analyses were adjusted for age and ethnicity to account for the sampling strategy, which was based on these variables. Age adjustment was accomplished using age as a continuous variable. Serum low-density-lipoprotein (LDL) cholesterol was related to serum lycopene and was thus adjusted for in the lipid-adjusted models by including LDL cholesterol as a continuous variable. These parameterizations were selected because they fit regression models on lycopene as well as or better than other parameterizations.

Pearson partial correlation coefficients were calculated to describe the relation between the dependent variable and continuous independent variables. Partial correlation coefficients were computed using the following two sets of adjustment variables: 1) age and ethnicity adjusted and 2) age, ethnicity, and lipid adjusted. All models containing diet-derived nutrients and individual food items were also adjusted for energy intake as estimated from the FFQ. For the relation between the dependent variable and categorical independent variables, linear regression models were used, and a P value for trend was calculated when appropriate. A stepwise multiple regression approach was used to select the final model. Statistical significance was defined as $p < 0.01$.

Results

The mean age of study participants was 61 years, and 44% were Caucasian, 37% were African American, 12% were Hispanic/Latina, and 7% were from other ethnic groups.

Serum lycopene was 0.40 ± 0.20 (SD) μg/ml and 0.071, 0.259, 0.364, 0.518, and 1.045 μg/ml for the 1st, 25th, 50th, 75th, and 99th percentiles of the distribution.

Table 1 gives the relationship between serum lycopene and other serum measures, adjusted for age and ethnicity. Serum LDL cholesterol was significantly correlated with serum lycopene ($r = 0.23$, adjusted for age and ethnicity). Serum total cholesterol was also associated with serum lycopene ($r = 0.22$); however, this association was no longer significant after adjustment for serum LDL cholesterol. For all other variables, adjustment for LDL cholesterol led to only small differences. After adjustment for age, ethnicity, and serum LDL cholesterol, serum lycopene concentrations were significantly positively correlated with serum β-carotene, serum α-carotene, serum β-cryptoxanthin, and serum lutein + zeaxanthin and significantly negatively correlated with serum γ-tocopherol. However, the magnitude of the associations was modest, and the correlation coefficients ranged from –0.10 to 0.18.

Dietary measures found to be significantly correlated with serum lycopene included total dietary lycopene, fresh tomatoes or tomato juice, cooked tomatoes, tomato sauce or salsa, green salad with vegetables, spaghetti with meat

Table 1. Association of Serum Lycopene With Serum Lipids and Serum Nutrients Among Participants in the Women's Health Initiative[a]

		Partial Correlations	
	n	r[b]	r[c]
Serum lipids			
LDL cholesterol	931	0.23*	
Total cholesterol	942	0.22*	0.02
Serum nutrients			
α-Tocopherol	945	0.11†	0.05
γ-Tocopherol	945	–0.03	–0.10†
β-Carotene	945	0.14*	0.15*
α-Carotene	946	0.18*	0.18*
Retinol	946	0.06	0.03
β-Cryptoxanthin	946	0.16*	0.13*
Lutein + zeaxanthin	946	0.11*	0.09†

a: Statistical significance is as follows: *, $p < 0.001$; †, $p < 0.01$.
b: r adjusted for age and ethnicity.
c: r adjusted for age, ethnicity, and low-density-lipoprotein (LDL) cholesterol.

Table 2. Association of Serum Lycopene With Dietary Lycopene, Foods Containing Lycopene, and Energy Intake Among Participants in the Women's Health Initiative[a]

Dietary Estimates	%[b]	Partial Correlation[c]
Dietary lycopene[d]		0.20*
Total fruits[d]		0.04
Total vegetables[d]		0.05
Tomatoes, fresh or juice[d]	89	0.11†
Tomatoes cooked, tomato sauce, salsa[d]	83	0.17*
Salad with vegetables[d]	82	0.09†
Watermelon and red melon[d]	49	0.07
Chili with meat and beans[d]	48	0.04
Spaghetti with meat sauce[d]	81	0.19*
Spaghetti with tomato sauce[d]	52	0.11†
Pizza[d]	65	0.03
Percent energy from fat		–0.06
Energy intake		–0.01

a: Statistical significance is as follows: *, $p < 0.001$; †, $p < 0.01$.
b: Percentage of participants consuming specified food frequency questionnaire item ≥1/mo.
c: Adjusted for age, ethnicity, and LDL cholesterol.
d: Adjusted for energy intake.

sauce, and spaghetti with tomato sauce (Table 2). Again, the associations were modest, with correlation coefficients of 0.09–0.20. We found no significant association between percent energy from fat and serum lycopene levels.

The results of simple linear regression analyses of serum lycopene with dietary, demographic, and lifestyle factors are given in Table 3. The coefficients can be interpreted as the magnitude of change in serum lycopene among those in the category of interest compared with those in the reference category, adjusted for age, ethnicity, and LDL cholesterol. Serum lycopene levels decreased significantly with age and body mass index (BMI). When these were treated as continuous variables, the partial correlations with serum lycopene were –0.17 with age and –0.15 with BMI. We observed a significant increase in serum lycopene levels with increasing alcohol consumption and income but no association with smoking.

Living in the southern region of the United States, compared with the northeastern region, was associated with having significantly lower serum lycopene levels. Compared with blood draws in the summer months, serum lycopene levels were significantly lower for blood draws during the fall, winter, and spring. Season of FFQ completion was not significantly associated with serum lycopene (data not presented).

Factors associated with serum lycopene in this study or in studies by others (except for other serum nutrients) were selected for entry as independent variables in stepwise multiple regression procedures (data not presented). We found that serum LDL cholesterol, age, BMI, dietary lycopene, season of blood draw, residing in the southern region vs. the northern region, and energy intake were independent predictors ($p < 0.01$) of serum lycopene. However, together these factors explained only 18% of the variation in serum lycopene values. With these factors in the model, income and alcohol were no longer associated with serum lycopene.

The variable expressing total dietary lycopene was replaced with individual food items high in lycopene and entered into the stepwise regression model discussed above (data not presented). In this model, we found that serum LDL cholesterol, cooked tomatoes, age, BMI, season of blood draw, residing in the southern region vs. the northern region, energy intake, and consumption of fresh tomatoes or tomato juice and spaghetti with meat sauce significantly explained variation in serum lycopene values ($R^2 = 0.20$).

Discussion

In this cross-sectional study of postmenopausal women, serum LDL cholesterol, other serum carotenoids, dietary intake estimates, and several participant characteristics were statistically significantly associated with serum lycopene levels. However, the magnitude of these associations was small, and overall these factors explained only a modest amount of the variability in serum lycopene levels.

Positive correlations of serum cholesterol and other serum carotenoids with serum lycopene levels have been reported (14,27,31). In this study, serum LDL cholesterol and lycopene were positively correlated, which occurs because lycopene is transported primarily in LDL (32). Serum lycopene was positively associated with the serum levels of all the other measured carotenoids. Because lycopene is found in relatively few fruits or vegetables, the association between serum lycopene and other carotenoids is unlikely to be the result of coconsumption of these compounds, and an absorptive link between lycopene and other carotenoids, particularly β-carotene, has been suggested (33).

Carotenoids in the circulating pool are thought to be largely unregulated (34) and directly reflect the dietary intake of these compounds (35–37). Nonetheless, we found only a weak association between dietary lycopene and serum lycopene, which was similar to what has been given in other reports (14,27,38). Given the small number of foods containing lycopene, it is not surprising that fruits and/or vegetables were not associated with serum lycopene, a finding consistent with the published literature (39,40).

The weak association between dietary lycopene and serum lycopene is partially a function of unmeasured variability in bioavailability of lycopene and individual differences in lycopene absorption, metabolism, and excretion (11,41). For example, it is believed that lycopene is more bioavailable in cooked than in raw tomato products, particularly if it is consumed with dietary fat (28). However, we saw no association of average fat intake with serum levels. Serum lycopene concentrations are also known to vary markedly after the consumption of identical quantities of lycopene because of variability in absorption (11).

Error in measuring dietary intake and serum measures of lycopene undoubtedly reduced our ability to explain variability in serum lycopene levels. Sources of error when estimating lycopene intake from an FFQ include poor reporting of diet, variability in the lycopene content of different types of tomatoes (10), differing food preparation techniques (11), or the lack of a sufficiently comprehensive inventory of foods on the FFQ. For example, ketchup is an important source of lycopene in the American diet because of the frequency of consumption (9), yet it is not assessed on the FFQ. In addition, although we altered the nutrient database to include updated values by Tonucci and co-workers (26), the accuracy of the database for lycopene is largely unknown.

Finally, the ability to detect and describe an association between dietary intake and serum levels of a nutrient is also influenced by the time span between the exposure and outcome assessment. An average of 35 days elapsed between completion of the FFQ and the blood draw. Therefore, it is possible that, with a smaller window of time between the two measures, the FFQ may have been a truer measure of serum lycopene. Alternatively, because supplementation with a lycopene-rich diet has been shown to increase serum lycopene levels only gradually (42), it is likely that multiple measures over a greater time interval may provide a more accurate estimate of serum lycopene.

We found that certain participant characteristics, health behaviors, and other factors were associated with serum

Table 3. Association of Serum Lycopene With Participant Characteristics, Health-Related Behavior, Geographic Region, and Season of Blood Draw Among Participants in the Women's Health Initiative

Independent Variable	*n*	%	Coefficient[a]	SE	*P* Value
Age, yr					
50–54	211	22			
55–59	243	26	–0.031	0.019	0.096
60–64	198	21	–0.061	0.020	0.002
65–69	174	18	–0.079	0.020	<0.001
70–79	120	13	–0.091	0.023	<0.001
					p (for trend) < 0.001
Ethnicity					
Caucasian	416	44			
African American	353	37	–0.020	0.014	0.154
Hispanic/Latina	110	12	0.036	0.021	0.089
Other	67	7	0.001	0.026	0.959
Education					
High school diploma/GED or below	235	25			
School after high school	379	40	0.001	0.016	0.938
College degree or higher	325	35	0.024	0.017	0.152
					p (for trend) = 0.127
Annual income					
<$20,000	199	22			
$20,000–$34,999	217	24	0.053	0.019	0.007
$35,000–$49,999	192	22	0.050	0.020	0.013
$50,000–$74,999	169	19	0.069	0.021	0.001
≥$75,000	116	13	0.096	0.024	<0.001
					p (for trend) < 0.001
Multivitamin use					
No	568	60			
Yes	378	40	–0.003	0.013	0.815
Alcohol					
Nondrinker or past drinker	340	36			
<1 drink/mth	139	15	0.034	0.020	0.090
<1 drink/wk	201	22	0.039	0.017	0.022
1 to <7 drinks/wk	187	20	0.065	0.018	<0.001
≥7 drinks/wk	68	7	0.071	0.026	0.006
					p (for trend) < 0.001
Smoking					
Never smoke	486	52			
Past smoker	373	40	–0.020	0.013	0.129
Current smoker	76	8	–0.045	0.024	0.061
Episodes of moderate or strenuous physical activity per week					
0	369	48			
1–2.0	131	17	0.037	0.021	0.074
2.5–4.0	135	18	0.026	0.020	0.206
≥4.5	128	17	0.043	0.021	0.042
					p (for trend) = 0.031
BMI,[b] kg/m^2					
<18.5	3	< 1			
18.5–24.9	203	21	0.192	0.112	0.086
25.0–29.9	320	34	0.177	0.112	0.113
30.0–34.9	253	27	0.129	0.112	0.250
35.0–39.9	117	12	0.119	0.113	0.292
≥40.0	50	5	0.101	0.115	0.379
					p (for trend) < 0.001
Geographic region					
Northeast	235	25			
South	295	31	–0.068	0.017	<0.001
Midwest	178	19	–0.027	0.019	0.165
West	238	25	–0.042	0.018	0.023
Season of blood draw					
Summer	220	23			
Fall	238	25	–0.062	0.018	<0.001
Winter	216	23	–0.063	0.019	<0.001
Spring	272	29	–0.061	0.018	<0.001

a: Coefficient from linear regression adjusted for age, ethnicity, and LDL cholesterol (see **Methods**).

b: Body mass index (BMI) categories on the basis of clinical guidelines from the Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults (43).

lycopene levels. These associations may result from metabolic differences, or they may reflect differences in eating patterns or other lifestyle factors that affect serum lycopene levels. Income and alcohol intake were associated with serum lycopene but were not independent predictors of serum lycopene in the stepwise regression model. However, age and BMI remained significant in the stepwise regression model, which included dietary intake. It is possible that these factors are proxies for dietary lycopene intake, which is poorly measured by FFQ and current databases.

Interest in lycopene as a preventive agent in disease has emerged only in the last 10 years. Lycopene and other carotenoids are well-known antioxidants and may have other biological activities, including upregulation of the cytochrome *P*-450 enzyme systems and enhancement of cell-to-cell communication (32). In this study, serum lycopene concentrations were poorly correlated with recent lycopene intake estimated by an FFQ. Our findings suggest several points for the interpretation of epidemiological studies of lycopene intake and cancer. First, it is likely that null studies cannot detect an association between serum lycopene and cancer risk because of dietary measurement error and the resultant inability to predict long-term serum levels. Studies that find an association between dietary lycopene and cancer risk may greatly underestimate the effect size. Alternatively, these associations may be due to other chemopreventive agents in tomatoes that are acting separately from lycopene. Finally, errors in quantifying dietary intake may result in identification of other factors (e.g., BMI) that are merely proxies for lycopene intake. In the absence of a large-scale clinical trial, we will need more precise dietary assessment instruments and a better understanding of the biological properties of carotenoids to understand the connection between lycopene and cancer risk.

Acknowledgments and Notes

This work was completed at The Women's Health Initiative Coordinating Center (Seattle, WA). The Women's Health Initiative is supported by National Institutes of Health Contract NO1-WH-2-2110. Address correspondence to Deborah Casso, Center for Health Studies, Suite 1600, Group Health Cooperative, 1730 Minor Ave., Seattle, WA 98101-1448.

Submitted 9 May 1999; accepted in final form 13 October 1999.

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