A Prospective Study of Tomato Products, Lycopene, and Prostate Cancer Risk

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Background: **Some data, including our findings from the Health Professionals Follow-Up Study (HPFS) from 1986 through January 31, 1992, suggest that frequent intake of tomato products or lycopene, a carotenoid from tomatoes, is associated with reduced risk of prostate cancer. Overall, however, the data are inconclusive. We evaluated additional data from the HPFS to determine if the association would persist.** ***Methods:*** **We ascertained prostate cancer cases from 1986 through January 31, 1998, among 47 365 HPFS participants who completed dietary questionnaires in 1986, 1990, and 1994. We used pooled logistic regression to compute multivariate relative risks (RR) and 95% confidence intervals (CIs). All statistical tests were two-sided.** ***Results:*** **From 1986 through January 31, 1998, 2481 men in the study developed prostate cancer. Results for the period from 1992 through 1998 confirmed our previous findings—that frequent tomato or lycopene intake was associated with a reduced risk of prostate cancer. Similarly, for the entire period of 1986 through 1998, using the cumulative average of the three dietary questionnaires, lycopene intake was associated with reduced risk of prostate cancer (RR for high versus low quintiles = 0.84; 95% CI = 0.73 to 0.96; P_{trend} = .003); intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater reduction in prostate cancer risk (RR for 2+ servings/week versus <1 serving/month = 0.77; 95% CI = 0.66 to 0.90; P_{trend}<.001), especially for extraprostatic cancers (RR = 0.65; 95% CI = 0.42 to 0.99). These associations persisted in analyses controlling for fruit and vegetable consumption and for olive oil use (a marker for Mediterranean diet) and were observed separately in men of Southern European or other Caucasian ancestry.** ***Conclusion:*** **Frequent consumption of tomato products is associated with a lower risk of prostate cancer. The magnitude of the association was moderate enough that it could be missed in a small study or one with substantial errors in measurement or based on a single dietary assessment. [J Natl Cancer Inst 2002;94:391–8]**

Among the more than 600 carotenoids in plants, only about 14 are found in human tissues *(1).* Tomato and tomato products contribute to nine of these 14 carotenoids and are the predominant source of lycopene, neurosporene, gamma-carotene, phytoene, and phytofluene. Because lycopene has potent antioxidant properties *(2),* studies have evaluated its potential anticancer effects, particularly against prostate cancer *(3).* The epidemiologic evidence based on dietary intake of lycopene or tomato products or circulating lycopene level has been mixed; six studies support a 30%–40% reduction in prostate cancer risk associated with high intakes *(4–9),* three studies are consistent with a similar reduction in risk *(10–12)* but the results were not statistically significant, and seven studies do not support an association *(13–19).* Thus, the association between tomato products or lycopene and prostate cancer risk, although suggestive, remains controversial.

Several factors may contribute to the apparent inconsistencies in the literature. First, the consumption of lycopene may be too low for a benefit in some populations. Second, dietary questionnaires may not have captured many potentially important contributors of lycopene nor accounted for its bioavailability, which varies profoundly for specific food items *(20–22).* Third, because prostate cancer develops over many decades, a single dietary measure may not necessarily adequately encompass the relevant period of carcinogenesis. Furthermore, prostate cancers are quite variable in regard to their aggressive potential, and possibly, lycopene may differentially influence more aggressive versus less aggressive cancers. Finally, confounding factors conceivably may have influenced relationships between lycopene and prostate cancer risk in some studies. For example, Cohen et al. *(18)* have argued that tomato products or serum lycopene levels may be markers for the intake of fruits and vegetables. Also, tomato products may represent part of an eating pattern, such as a Mediterranean diet consumed in Southern European populations.

In 1995, we reported an association between higher intake of lycopene and tomato products and lower risk of prostate cancer from a prospective study of male health professionals *(5).* The first study report was based on a single dietary assessment with follow-up from 1986 through January 31, 1992, and on 773 incident cases of prostate cancer. To address the issues raised above, we now report results based on multiple dietary assessments from 1986 to 1998 and on 2481 cases of prostate cancer.

Subjects and Methods

The Study Population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study of 51 529 U.S. male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians aged 40–75 years in 1986. At baseline, these men responded to a mailed questionnaire, which elicited information on age, marital status, height and weight, ancestry, medications, smoking history, disease history, physical activity, and diet (described below). To generate the physical activity score, we summed activity-specific MET-hours/week for reported activities, using MET values based on a compendium of activities. One MET-hour is the metabolic equivalent of sitting at rest for 1 hour.

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See "Notes" following "References."

Follow-up questionnaires sent to the entire cohort in 1988, 1990, 1992, 1994, 1996, and 1998 ascertained new cases of a variety of diseases, including cancers, and updated exposure information. Most of the deaths in the cohort were reported by family members or by the postal system in response to the follow-up questionnaires. In addition, we used the National Death Index to ascertain fatalities among nonrespondents. Through the various methods, we estimate ascertaining over 98% of the deaths in this cohort. This study received institutional approval by the Human Research Committee at the Harvard School of Public Health. Completion of the self-administered questionnaire was considered to imply informed consent.

The Semiquantitative Food-Frequency Questionnaire

We used a semiquantitative food-frequency questionnaire to assess diet [described in detail in *(23)*]. The 1986 questionnaire contained a list of 131 food and beverage items. For each item listed, a commonly used unit or portion size was specified, and participants were asked how often, on average, over the past year, they consumed that amount of each food. Participants chose from among nine possible responses for frequencies, which ranged from never to six or more times per day. We also queried about the brand of breakfast cereal; the duration, frequency, and brand of multivitamin and individual vitamin supplement use; and the types of fat commonly used in cooking, frying, and at the table. The dietary questionnaire also included an open-ended section for unlisted foods. A similar dietary questionnaire was administered to the cohort in 1990 and in 1994.

We computed nutrient intakes by multiplying the consumption frequency of each unit of food by the nutrient content of the specified portions, using composition values from U.S. Department of Agriculture (USDA) sources supplemented with other data. We updated our nutrient database for carotenoid values using the USDA–National Cancer Insitute database *(24,25)*. We recently updated the carotenoid content of tomato-based food products with values from the USDA, which were derived from reversed-phase high-performance liquid chromatography *(21)*. These updates have substantially increased the estimated lycopene intake in our population from previous reports, but the ranking of individuals has not been altered appreciably *(5)*. Food contributors to lycopene in our 1986 questionnaire include tomatoes, tomato sauce, tomato juice, pizza, watermelon, and pink grapefruit. Questionnaires in 1990 and 1994 have also considered salsa, picante or taco sauce, and ketchup or red chili sauce.

In 1986, we evaluated the validity of nutrient and food consumption measured by the questionnaire among a sample of 127 cohort members from the Boston area *(23,26)*. The mean correlation coefficients between intakes determined by two 1-week diet records and the dietary questionnaire (adjusting for week-to-week variation in the diet records) were 0.65 for nutrients and 0.63 for specific foods. The correlation between computed dietary intake of lycopene and plasma concentration of lycopene (adjusted for age, body mass index [BMI], plasma cholesterol, and plasma triglycerides) was 0.46 *(27)*. Among specific food items, tomato sauce had the strongest correlation ($r = 0.37$).

Identification of Cases of Prostate Cancer

On each of the follow-up questionnaires that were mailed every 2 years, we asked the participant whether he had had a diagnosis of prostate cancer during the previous 2 years. The response rate averaged 94% for biennial follow-up questionnaires through 1998. When the participant (or next of kin for decedents) reported a diagnosis of prostate cancer, we asked for permission to obtain hospital records and pathology reports to confirm the diagnosis and obtain further details. Study physicians used the information received from any procedures or tests conducted during the initial diagnosis, including staging prostatectomy and bone scans, to stage the prostate cancer cases.

From 1986 to the end of this study period (January 31, 1998), after we excluded 55 cases of stage T1a cancers (incidental histologic cancer found in 5% or less of tissue resected) *(28)*, we documented 2481 cases of prostate cancer. The stage T1a lesions were excluded because these are relatively innocuous and are especially prone to detection bias. Because stage T1a cancers encompass only 2% of the total cases, the influence of this exclusion on the results was minimal. We documented the endpoint with the use of medical records and pathology reports for 89% of the 2481 cases; for the majority of the remainder, men provided information regarding the basis of diagnosis and subsequent treatment; 2.6% of the case patients could not be recontacted or refused to provide further information.

Data Analysis

Before we conducted any analyses, we excluded men who reported cancer at baseline (other than nonmelanoma skin cancer). We also excluded men (3%) who did not adequately complete the dietary questionnaire (70 or more items left blank or reported intake of more than 17 600 joules [4200 kcal] or less than 3350 joules [800 kcal] per day). The remaining 47 365 participants were followed from the month of return of the baseline questionnaire to the month of diagnosis of prostate cancer, the month of death from other causes, or the end of the study period (January 31, 1998). The major endpoint for analysis was any new diagnosis of prostate cancer (excluding stage T1a tumors) in the cohort up to January 31, 1998. We also considered as separate groups for analyses organ-confined prostate cancer and cancers extending locally into other organs and metastatic disease (including fatal cancers during the follow-up period).

The major dietary exposures we considered were total lycopene intake, tomato sauce intake, and an empirical lycopene bioavailability score. This score weighs lycopene-containing items differentially on the basis of coefficients from a stepwise linear regression model using lycopene-containing foods from the food frequency questionnaire to predict plasma lycopene levels *(29)*. We used the sample of 121 cohort members who provided blood samples to compute the coefficients. This score, in part, accounts for differential bioavailability of lycopene across items. We adjusted nutrient values for total energy intake using a regression analysis *(30)*. For tomato sauce and the lycopene score, we adjusted for energy intake by including caloric intake in multivariate models.

We calculated the incidence of prostate cancer among study participants for each quintile of lycopene intake or empirical lycopene score intake by dividing the number of incident cases by the number of person-years in that quintile. The relative risk (RR) for each of the upper four quintiles of intake was computed as the rate among men in each of the upper quintiles divided by the rate among men in the lowest quintile of intake. Similar analyses were conducted for tomato sauce, on the basis of prespecified categories of intake. We used the Mantel–Haenszel summary estimator to adjust for age (across 5-year categories).

We used pooled logistic regression models for failure-time data *(31)* to control for multiple variables simultaneously (*see* footnote to tables for covariates adjusted for) and to compute 95% confidence intervals (CIs). These models have been shown to closely approximate models based on the Cox partial likelihood function as long as the disease is rare within successive (2-year) questionnaire cycles *(31,32)*. We conducted tests for trends across categories controlling for multiple covariates by modeling the median values of quintiles or categories of dietary intake as a continuous variable in the multivariate model. All reported *P* values are two-sided. All analyses were conducted using SAS release 6.12 (SAS Institute, Inc., Cary, NC).

For analyses based on the entire 1986 through January 31, 1998, follow-up period, we used the data from the multiple dietary questionnaires in three ways. First, baseline (1986) exposure was used without updating to maximize the influence of a longer induction period between dietary intake and period of risk. Second, we used simple updating, characterizing the period of risk by use of the proximal prior questionnaire to maximize recent influences of diet. Third, we used cumulative average updated analysis to minimize within-person random variation and to compute the best assessment of average long-term intake based on all the available questionnaires *(33)*. In this approach, we used the 1986 intakes between 1986 and 1990; the simple average of the 1986 and the 1990 intakes to prospectively predict outcomes between 1990 and 1994; and the simple average of the 1986, 1990, and 1994 intakes to prospectively predict outcomes between 1994 and 1998.

For the February 1992 through January 31, 1998, follow-up period, we used cumulative updating including the 1986 questionnaire to provide the best estimate of long-term intake of lycopene and tomato sauce. In an additional analysis, we used only the 1990 questionnaire and the February 1992 through January 1998 follow-up period to examine whether we could replicate the initial findings, which were based on the 1986 dietary assessment and the 1986 through January 1992 follow-up period, using an independent dietary questionnaire and independent follow-up data.

RESULTS

Lycopene Intake and Risk of Prostate Cancer: Updated Analysis

We previously reported *(5)* that lycopene intake in 1986 was associated with a reduced risk of prostate cancer from 1986 through 1992 (RR for high versus low quintile of intake = 0.79; 95% CI = 0.64 to 0.99; P_{trend} = .04). In the new analyses from 1992 to 1998, based on the cumulative average updated dietary lycopene, we found similar results for lycopene intake (RR for high versus low quintile of intake = 0.83; 95% CI = 0.70 to 0.98; P_{trend} = .02). We then examined the entire follow-up period (from 1986 through 1998) (Table 1). We found little evidence of an association between lycopene intake and reduced risk of prostate cancer using only the baseline (1986) questionnaire. However, we found statistically significant associations between lycopene intake and reduced risk of prostate cancer when using the simple or the cumulative updated assessment. When examining extreme deciles rather than quintiles, the association between lycopene intake and risk of prostate cancer was slightly stronger (RR for cumulative average intake = 0.78; 95% CI = 0.65 to 0.94). Results for the age-adjusted analyses were essentially identical to those based on the full multivariate model; thus, we present only the multivariate RRs.

Influence of Bioavailability of Lycopene

We found that people who have a high tomato sauce intake, the strongest predictor of plasma lycopene, were at reduced risk of prostate cancer from 1992 through January 31, 1998 (cumulative average updated RR for 2+ servings/week versus <1 serving/month = 0.79; 95% CI = 0.64 to 0.97; P_{trend} <.001). In a separate analysis, we used the 1990 questionnaire on dietary

Table 1. Relative risk (RR) of prostate cancer and 95% confidence intervals (CI) among members of the Health Professionals Follow-up Study, free of cancer at baseline and followed for 12 years (1986–1998)

	Lycopene intake (quintiles)*					
	Q1	Q2	Q3	Q4	Q5	P_{trend}†
Baseline‡						
Person years	102 567	103 746	103 134	103 141	102 613	
Cases	511	486	498	507	479	
RR§	1.0	1.01	1.02	1.02	0.94	.39
CI		0.89 to 1.15	0.90 to 1.16	0.90 to 1.16	0.83 to 1.08	
Simple updated‡						
Person years	102 257	103 395	102 334	103 109	104 106	
Cases	562	495	479	492	453	
RR§	1.0	0.96	0.91	0.96	0.84	.02
CI		0.85 to 1.09	0.81 to 1.03	0.84 to 1.08	0.74 to 0.96	
Cumulative average updated‡						
Person years	101 736	103 521	103 864	103 416	102 665	
Cases	523	519	504	497	438	
RR§	1.0	1.03	0.99	0.97	0.84	.003
CI		0.91 to 1.17	0.87 to 1.12	0.86 to 1.11	0.73 to 0.96	

*The median values of lycopene intake for quintiles 1–5 in 1986 were 3415, 6156, 8663, 12 198, and 18 780 micrograms/day.

†*P* for trend is based on Wald statistic and is two-sided.

‡Baseline used 1986 diet questionnaire only; simple updated used most recent questionnaire (1986, 1990, 1994) only; cumulative average updated used the average of all the diet questionnaires available to that point in the follow-up period.

§RR adjusted for age (5-year categories), time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid.

intake to examine the risk of prostate cancer between 1992 and 1998 to assess whether using entirely independent exposure and follow-up data from our previous report confirmed the earlier results. The relative risk and confidence intervals (RR = 0.80; 95% CI = 0.64 to 1.00; P_{trend} = .02) were similar to those previously reported *(5)*. For the entire 1986 through January 31, 1998, follow-up, we found statistically significant inverse associations using the baseline, simple updated, and cumulative updated analyses (Table 2). For the baseline analysis, only the top category (2+ servings per week) was statistically significant (RR = 0.75; 95% CI = 0.64 to 0.88), whereas for the updated analyses, a benefit was apparent even for one serving per week (RR = 0.80; 95% CI = 0.70 to 0.91). Using the empirical lycopene score, which is heavily weighted toward tomato sauce, we found results similar to those for tomato sauce intake (RR for the highest versus the lowest quintile = 0.76; 95% CI = 0.60 to 0.96; P_{trend} <.001).

Age at Diagnosis

The association between tomato sauce intake and reduced risk of prostate cancer was weak, if present at all, for men diagnosed when younger than 65 years of age (RR cumulative average updated for 2+ servings/week versus <1 serving/month = 0.89; 95% CI = 0.67 to 1.17; P_{trend} = .20; n = 807 cases) and strong for men diagnosed when 65 years or older (RR = 0.69; 95% CI = 0.56 to 0.84; P_{trend} = .001; n = 1674 cases). However, among men over 65 years of age, the association between tomato sauce intake and reduced risk of prostate cancer did not strengthen with increasing age.

Stage of Disease

We found similarly sized reductions in risk for organ-confined prostate cancer, cancers that had progressed locally into the adjacent organs or further, and cancers that were metastatic at diagnosis or fatal by the end of follow-up (Table 3). In analyses limited to the 1992 through January 31, 1998, follow-up, we found similar patterns, most notably with a marked reduction in risk of metastatic cancers (RR cumulative average updated for 2+ servings/week versus <1 serving/month = 0.34; 95% CI = 0.13 to 0.90; P_{trend} = .01; n = 95 cases).

Confounding Factors

We controlled for dietary variables related to risk of prostate cancer in this population because these may be confounders (factors associated with the factor of interest that are independent predictors of risk). Multivariate analyses indicated no appreciable confounding between lycopene or tomato sauce intake and prostate cancer risk. Other variables, including body mass index (weight divided by height squared), aspirin use, marital status, ancestry, geographic region of residence, level of physical activity, vasectomy, smoking habits, and alcohol use also were not confounders.

We also considered whether the association with tomato intake was not direct but rather from tomato intake being part of or a surrogate for a beneficial Mediterranean dietary pattern. We first examined whether a reduced risk of prostate cancer occurred only in men of Southern European ancestry. Although an association was seen between tomato sauce intake and reduced risk of prostate cancer among men of Southern European ancestry, a similar association was also observed among men of other Caucasian ancestry (Table 4). Individual analysis of the other groups (Scandinavian ancestry, Asian Americans, African Americans, and others) was not possible because of small sample sizes. In addition, we also controlled for olive oil as "usual type of cooking oil" to examine further whether tomato sauce was part of the Mediterranean dietary pattern and found that the association between tomato sauce intake and reduced prostate cancer risk did not change (Table 4). Moreover, using factor analysis we could not identify any dietary pattern with tomato sauce as an important component that was more strongly related to prostate cancer risk than was tomato sauce alone. In addition, we controlled for total fruit and vegetable consumption

Table 2. Relative risk (RR) of prostate cancer and 95% confidence intervals (CI) among members of the Health Professionals Follow-up Study, free of cancer at baseline and followed for 12 years (1986–1998)

	Tomato sauce intake (servings)				
	<1/month	1–3/month	1/week	⩾2/week	P_{trend}*
Baseline†					
Person years	97 305	189 415	159 337	69 144	
Cases	653	973	632	223	
RR‡	1.0	0.92	0.94	0.75	<.001
CI		0.83 to 1.02	0.84 to 1.05	0.64 to 0.88	
Simple updated†					
Person years	91 612	187 205	162 194	74 189	
Cases	601	1014	611	255	
RR‡	1.0	0.99	0.89	0.84	.01
CI		0.90 to 1.10	0.79 to 1.00	0.72 to 0.99	
Cumulative average updated†					
Person years	68 264	207 495	153 532	85 910	
Cases	437	1182	567	295	
RR‡	1.0	0.96	0.80	0.77	<.001
CI		0.85 to 1.07	0.70 to 0.91	0.66 to 0.90	

*P for trend is based on Wald statistic and is two-sided.

†Baseline used 1986 diet questionnaire only; simple updated used most recent questionnaire (1986, 1990, 1994) only; cumulative average updated used the average of all the diet questionnaires available to that point in the follow-up period.

‡RR adjusted for age (5-year categories), time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid.

Table 3. Relative risk (RR) of prostate cancer and 95% confidence intervals (CI) among members of the Health Professionals Follow-up Study, free of cancer at baseline and followed for 12 years (1986–1998)

	Tomato sauce intake (servings)*				
	<1/month	1–3/month	1/week	⩾2/week	P_{trend}†
Person years	68 264	207 495	153 532	85 910	
Organ-confined‡					
Cases	237	630	277	176	
RR§	1.0	0.86	0.63	0.72	<.001
CI		0.74 to 1.0	0.53 to 0.76	0.59 to 0.89	
Advanced‡					
Cases	72	174	74	34	
RR§	1.0	0.99	0.77	0.65	.02
CI		0.75 to 1.31	0.55 to 1.08	0.42 to 0.99	
Metastatic‡					
Cases	59	141	53	25	
RR§	1.0	1.06	0.77	0.64	.03
CI		0.78 to 1.44	0.52 to 1.12	0.39 to 1.05	

*Tomato sauce intake based on cumulative average updated, which used the average of all the diet questionnaires available to that point in the follow-up period.

†*P* for trend is based on Wald statistic and is two-sided.

‡Organ-confined are cancers with no evidence of extraprostatic involvement at time of diagnosis; advanced cancers are those with involvement of adjacent organs or metastatic; metastatic cancers include all fatal cancers by 1998, as well as those with pelvic lymph node or distant metastasis.

§RR adjusted for age (5-year categories), time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid.

Table 4. Relative risk (RR) of prostate cancer and 95% confidence intervals (CI) among members of the Health Professionals Follow-up Study, free of cancer at baseline and followed for 12 years (1986–1998)

	Tomato sauce intake (servings)*				
	<1/month	1–3/month	1/week	⩾2/week	P_{trend}†
Southern European ancestry (528 cases)					
RR‡	1.0	1.14	0.91	0.66	.002
CI		0.87 to 1.49	0.68 to 1.23	0.47 to 0.93	
Other Caucasian ancestry (1474 cases)					
RR‡	1.0	0.90	0.77	0.79	.005
CI		0.78 to 1.03	0.65 to 0.91	0.65 to 0.98	
Controlling for olive oil preference (2481 cases)					
RR§	1.0	0.96	0.80	0.77	<.001
CI		0.85 to 1.07	0.70 to 0.91	0.66 to 0.91	
Controlling for fruit and vegetable intake (2481 cases)					
RR‖	1.0	0.96	0.80	0.78	<.001
CI		0.86 to 1.07	0.70 to 0.92	0.66 to 0.91	

*Tomato sauce intake based on cumulative average updated, which used the average of all the diet questionnaires available to that point in the follow-up period.

†*P* for trend is based on Wald statistic and is two-sided.

‡RR adjusted for age (5-year categories), time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid.

§RR controlled for all covariates (age [5-year categories], time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid) and additionally for use of olive oil as typical oil for cooking.

‖RR controlled for all covariates (age [5-year categories], time period, ancestry, body mass index at age 21, and intakes of total energy, calcium, phosphorus, fructose, vitamin D, vitamin E, total fat, and α-linolenic acid) and additionally for total fruit and vegetable intake (quintiles).

in our multivariate model and found the effect of tomato sauce unchanged (Table 4). Total fruit and vegetable consumption, as in our earlier follow-up, was unrelated to the risk of prostate cancer (P_{trend} = .15).

Detection Bias

In recent years, although screening for prostate-specific antigen (PSA) has become widespread in the United States, it is unlikely to have influenced our results because frequency of PSA screening did not vary by frequency of tomato sauce consumption. Among infrequent consumers of tomato sauce, 67.9% of men had had a PSA test by 1998, compared with 68.4% for frequent consumers. In addition, the inverse association between tomato sauce intake and prostate cancer risk persisted in an analysis based on a follow-up from 1994 to 1998 that was restricted to men who had a recent PSA test before baseline (within 2 years of 1994; RR 2+ servings/week versus <1 serving/month = 0.85; 95% CI = 0.60 to 1.19; P_{trend} = .05; n = 646 men with prostate cancer). Among the men without a baseline PSA test (n = 359 with prostate cancer), the RR for high versus low tomato sauce intake was 0.79 (95% CI = 0.45 to 1.40; P_{trend} = .06). Thus, similar associations were seen between tomato

sauce intake and reduced prostate cancer risk in men screened or unscreened at baseline before follow-up for elevated PSA.

Discussion

We have confirmed an earlier reported *(5)* association between lycopene and tomato sauce intake and a reduced risk of prostate cancer in the HPFS. The initial observation was based on 773 case patients from 1986 to 1992; we then analyzed 2481 case patients from 1986 to 1998. Our findings were highly unlikely to result from chance because similar associations were observed regarding tomato sauce intake and reduced risk of prostate cancer for independent time periods using different questionnaires. Recall bias is unlikely in a prospective study. PSA screening use was uniform across levels of tomato sauce intake, and restricting analysis to men who had PSA tests did not change the results. Thus, appreciable detection bias probably did not occur.

Although uncontrolled confounding by unaccounted factors or by imprecise measurement of assessed factors cannot be entirely excluded, several factors argue strongly against the possibility that this materially influenced our results. Multivariate analyses yielded results similar to those from age-adjusted analyses. Tomato sauce was a relatively small component of the diet and was not strongly associated with other dietary and lifestyle factors. For example, current smoking status (9.6% of infrequent tomato sauce consumers versus 8.6% of frequent consumers), average alcohol intake (10.1 g/day versus 11.9 g/day), body mass index (25.5 kg/m^2 versus 25.7 kg/m^2), leisure time physical activity (19.3 MET-hours/week versus 21.8 MET-hours/week), and total saturated fat intake (24.9 g/day versus 22.7 g/day) differed only slightly between infrequent and frequent consumers of tomato sauce. Also, when we controlled for total vegetable and fruit intake, the findings with tomato sauce were unaltered. Associations between tomato sauce and reduced risk of prostate cancer were observed both for men of Southern European ancestry and of other Caucasian ancestry and when we controlled for olive oil use as a marker of a Mediterranean dietary pattern.

Our findings support a role for tomato-based products in decreasing the risk of prostate cancer and may help explain some of the apparent inconsistencies in the literature. The magnitude of the association is moderate and could easily be missed in a small study. For bioavailable lycopene, measurement error is likely to be substantial in many studies. In studies that have compared dietary lycopene intake with circulating levels *(32–43)*, correlations have generally been about 0.2. In our cohort, we reported *(26)* the highest published correlation between dietary and circulating lycopene ($r = 0.46$). In our study, the item tomato sauce captures most of the bioavailable lycopene. Tomato sauce is an ideal source of lycopene because it is highly concentrated in this carotenoid, the thermal processing disrupts lycopene from binding matrices, and the oil base makes the highly lipophilic lycopene available to micelles necessary for intestinal absorption.

In addition to the large study size and accounting for bioavailability, the repeated measurement of diet was critical in determining the association between lycopene intake and risk of prostate cancer. Although baseline lycopene intake alone was inversely related to risk of prostate cancer in the subsequent 6-year interval, the association was not statistically significant when extended to the total 1986 to 1998 follow-up period. Without updating dietary information, we would have missed the association with total lycopene intake and with more moderate consumption of tomato sauce (one serving per week). Even with our updated dietary measures, the inherent difficulty of measuring lycopene indicates that, if this association is causal, the magnitude of the benefit may be even stronger than observed because a substantial proportion of the variation in plasma lycopene is unexplained by dietary intake *(26)*.

The studies that have examined tomato product or lycopene intake or circulating lycopene levels in relation to prostate cancer risk can be summarized as follows: Those that support a statistically significant inverse association *(4–9);* those consistent with an approximately 30% reduction in risk but that were not statistically significant *(10–12);* and those that are nonsupportive *(13–19)*. In at least three of the nonsupportive studies *(13,15,19)*, intake of tomato products or sources of bioavailable lycopene may have been too low to be informative. In addition, a British study *(14)* showed an inverse association with baked beans, leading the authors to speculate that the tomato paste in canned baked beans, a good source of bioavailable lycopene, may have accounted for this association. The results from an additional study *(44)* were equivocal, showing a statistically significant inverse association with tomato consumption but not with lycopene intake.

The largest blood-based study *(8)* was a nested case–control study using frozen samples collected from 14 916 male physicians in 1982. Over 13 years of follow-up, 578 prostate cancer cases were ascertained, including 259 classified as "aggressive" on the basis of high grade or advanced stage. A low risk of prostate cancer was observed, particularly for aggressive prostate cancer (RR of high versus low quintile of plasma lycopene = 0.56; 95% CI = 0.34 to 0.92). By contrast, in the serum-based study by Nomura et al. *(15)*, no association was observed between baseline serum lycopene concentration and prostate cancer risk. Two factors may have contributed to these null results. First, a single assessment of serum lycopene was used to characterize follow-up for a period of up to 22 years (only 14 cases occurred within the first 5 years of follow-up). In the HPFS, results were stronger with updated than with baseline lycopene intake, suggesting that recent intake is more important than remote intake. Also, the serum lycopene levels were quite low—the median serum concentration among controls was only 134 ng/mL, compared with 424 ng/mL in the HPFS sample *(5)* and 388 ng/mL in the Physicians' Health Study *(8)*. The low levels may reflect very low levels of bioavailable lycopene consumed in that population by participants in the study by Nomura et al *(15)*. Three recently published nonsupportive case–control studies *(16–18)* conducted in North America, where tomato product intake is generally high, apparently had reasonably comprehensive assessments of tomato product intakes, but how well these captured true variation of lycopene levels was not assessed. As discussed above, because dietary questionnaires do not always capture true variation in the lycopene status in a given population, null studies should be interpreted cautiously.

One of these studies, conducted in Seattle, merits particular consideration *(18)*. In that study, a suggestive inverse association was observed for cooked tomatoes (RR [adjusted for covariates] for ⩾3 versus <1 serving per week = 0.73; 95% CI = 0.48 to 1.10; $P_{trend} = .13$). However, this inverse association was attenuated when additionally controlled for intake of total fruits or vegetables (RR = 0.90), leading Cohen et al. *(18)* to

argue that in previous studies, tomato products or serum lycopene levels may have been confounded by consumption of total fruits and vegetables. In the current HPFS study, fruit and vegetable consumption did not confound the results. Moreover, total fruit and vegetable intake has generally not been related to prostate cancer risk nor to lycopene level *(27,36,43)*, so it is unlikely to be a major confounder. The case–control study *(18)* was restricted to men under the age of 65. Interestingly, we did not observe a substantial association between lycopene intake and prostate cancer risk in men under the age of 65 years in the HPFS, based on 805 cases. Possibly, prostate cancers presenting at an early age may represent an accelerated process of carcinogenesis influenced more by genetic or endogenous factors and perhaps by other exogenous factors.

Overall, data suggest that the intake of tomatoes and tomato products is associated with a decreased risk of prostate cancer. This benefit may be related to the antioxidant properties of lycopene, but other potential mechanisms and other beneficial tomato-based components instead of or combined with lycopene cannot be excluded *(45)*. Of note, the survival of rats with prostate cancer induced by *N*-methyl-*N*-nitrosurea and testosterone was increased slightly by lycopene supplementation (17% increase; $P = .16$) but more so by tomato powder (39% increase; $P = .0056$) *(46)*. Because current evidence is not definitive, other lines of evidence are needed to provide confirmatory information. A long-term large randomized trial with prostate cancer as the endpoint would be most informative, but short-term trials using endpoints such as prostate cancer recurrence or intermediate endpoints may be more feasible. On the basis of our results, future epidemiologic studies, to be maximally informative, should examine populations with relatively high intakes of tomato products, be sufficiently large to evaluate moderate relative risks, have a comprehensive assessment of major lycopene sources, account for bioavailability of lycopene, account for temporal patterns (as a single dietary or blood assessment, particularly in studies with long follow-up periods, may be inadequate), and examine a wide range of age groups.

From the available data, we suggest that increased consumption of tomato and tomato-based products may be prudent; such a recommendation is consistent with current health guidelines to increase fruit and vegetable consumption. Efficacy and safety of pills containing only lycopene, however, would need to be specifically evaluated.

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