# A Prospective Study of Lycopene and Tomato Product Intake and Risk of Prostate Cancer

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## Abstract

Background: **Dietary lycopene and tomato products may reduce risk of prostate cancer; however, uncertainty remains about this possible association.**
Methods: **We evaluated the association between intake of lycopene and specific tomato products and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a multicenter study designed to investigate cancer early detection methods and etiologic determinants. Participants completed both a general risk factor and a 137-item food frequency questionnaire at baseline. A total of 1,338 cases of prostate cancer were identified among 29,361 men during an average of 4.2 years of follow-up.**
Results: **Lycopene intake was not associated with prostate cancer risk. Reduced risks were also not found for total tomato servings or for most tomato-based foods. Statistically nonsignificant inverse associations were noted for pizza [all prostate cancer: relative risk (RR), 0.83; 95% confidence interval (95% CI), 0.67-1.03 for ≥1 serving/wk versus < 0.5 serving/mo; $P_{trend}$ = 0.06 and advanced prostate cancer: RR, 0.79; 95% CI, 0.56-1.10; $P_{trend}$ = 0.12] and spaghetti/tomato sauce consumption (advanced prostate cancer: RR = 0.81, 95% CI, 0.57-1.16 for ≥2 servings/wk versus < 1 serving/mo; $P_{trend}$ = 0.31). Among men with a family history of prostate cancer, risks were decreased in relation to increased consumption of lycopene ($P_{trend}$ = 0.04) and specific tomato-based foods commonly eaten with fat (spaghetti, $P_{trend}$ = 0.12; pizza, $P_{trend}$ = 0.15; lasagna, $P_{trend}$ = 0.02).**
Conclusions: **This large study does not support the hypothesis that greater lycopene/tomato product consumption protects from prostate cancer. Evidence for protective associations in subjects with a family history of prostate cancer requires further corroboration.** (Cancer Epidemiol Biomarkers Prev 2006;15(1):92–8)

## Introduction

Older men, African Americans, and men with a family history of prostate cancer are at greater risk for prostate cancer (1, 2). Among the potential dietary determinants of this disease, attention has focused on tomato products and a major tomato constituent, lycopene, as possible protective agents. Lycopene and/or tomatoes have been inversely related to prostate cancer risk in prospective (3, 4) and case-control interview studies (5-9) and in serum-based investigations (refs. 10-13; with five studies reaching statistical significance, refs. 3, 4, 6, 7, 12). A number of investigations, however, have not supported this result, including prospective (14) and case-control interview studies (15-20) and serum-based studies (21, 22). Overall, the epidemiologic evidence suggests that tomato products and lycopene may reduce prostate cancer risks by 10% to 20% (23), with potentially greater protection observed for advanced prostatic cancer (4, 11, 13).

Tomatoes and tomato products are rich sources of folate, vitamin C, potassium, and carotenoids and contain vitamin E, vitamin A, flavonoids, and phytosterols, among other components (24). The most abundant of the phytonutrients in tomatoes are the carotenoids, with lycopene being the most prominent (tomatoes representing 80% of U.S. lycopene intake, ref. 25; ref. 24). Lycopene is not converted to vitamin A, as are many of the carotenoids; it is, however, a particularly potent antioxidant (26, 27) and may have other anticarcinogenic properties (28). Because lycopene is extremely lipophilic (orders of magnitude more so than most other fat-soluble antioxidants; ref. 29), its bioavailability is enhanced when cooked and consumed in oil media, such as tomato paste, tomato sauce, or pizza (30). Therefore, its biological effect may vary according to the specific food source and preparation method (31).

We studied the relationship between tomato and lycopene intake and prostate cancer risk among participants in the screened arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, which was designed to evaluate the effect of screening for these cancers on disease-specific mortality, and to identify etiologic determinants of cancer (32, 33). Although this approach has led to the study of tumors that would not necessarily have come to clinical attention without screening, differential early detection by dietary profile was in essence eliminated as a possible confounder of the diet-disease association.

We studied almost 30,000 men, including >1,300 cases of prostate cancer, allowing for stratification of results by tumor subtype. We prospectively collected detailed information on tomato and lycopene consumption, specifically to address this hypothesis.

## Materials and Methods

**Study Setting.** The Prostate, Lung, Colorectal, and Ovarian Trial was a multicenter study (Birmingham, AL; Denver, CO;

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Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC) in which participants were enrolled from November 1, 1993 to June 30, 2001 (33). The trial recruited men and women from the general population, by direct mailings, advertisements, and other means. Men ages 55 to 74 years were eligible for the trial if they had no history of prostate, colon, or lung cancer; were not under treatment for cancer (excluding nonmelanoma skin cancer); did not have surgical removal of the prostate, one lung, or the colon; had not taken finasteride in the past 6 months; had no more than one prostate-specific antigen (PSA) test in the past 3 years; and were not participating in another screening or cancer prevention trial. Study participants provided written informed consent, after approval by the institutional review boards of the U.S. National Cancer Institute and the 10 screening centers.

Men randomized to the screening arm of the trial underwent prostate cancer early detection by serum PSA (at entry and annually for 5 years) and digital rectal examination (at entry and annually for 3 years). Men with a PSA test result of >4 ng/mL or digital rectal examination suspect for prostate cancer were referred to their medical care providers for prostate cancer diagnostic evaluation. In addition, trial participants were requested to provide information about recent diagnoses of cancer through annual mailed questionnaires.

Medical and pathologic records related to the diagnosis were obtained for participants suspect for prostate cancer by screening or annual questionnaire. For deaths, death certificates and supporting medical/pathologic records were also collected. Data related to cancer diagnosis and death were abstracted by trained medical abstractors, including systematic quality control review on a sample of participants. Staging procedures corresponded to the tumor-node-metastasis stage of disease classification (34) and were based on clinical (57%) or clinical and surgical findings (43%). Gleason scores were assigned the highest reported value, based on biopsy and prostatectomy results.

**Study Population.** Of the 38,352 men randomized to the screening arm of the trial, we excluded men reporting a history (before study entrance) of cancer, other than nonmelanoma skin cancer ($n$ = 1,001), men who did not have a baseline PSA test or digital rectal examination ($n$ = 2,530), men who received a baseline screening exam but for whom there was no subsequent contact ($n$ = 1,045), men who did not complete a baseline risk factor questionnaire ($n$ = 903), and men who did not provide a dietary questionnaire ($n$ = 6,604; 83% response rate) or missed more than seven items on the food frequency questionnaire ($n$ = 250) or reported energy intake in the top or bottom 1% of the reported energy intake distribution ($n$ = 634). We also excluded men whose first valid screen occurred after October 1, 2001, the censor date for the current analysis ($n$ = 155). After exclusions, the analytic cohort comprised 29,361 men (some participants fell in multiple exclusion categories), predominately Whites (90.7%), followed by Asian/Pacific Islanders (4.0%), African Americans (3.3%), Hispanics (1.8%), and American Indians/Alaskan Natives (0.2%).

**Procedures.** At study entry (baseline), participants provided information by questionnaire on age, race, education, height and weight, brief occupational history, smoking status and quantity, family medical history (including family history of prostate cancer), personal medical history (including selected medication use), and physical activity.

Dietary information was collected through a self-administered, semiquantitative food frequency questionnaire (FFQ; http://www3.cancer.gov/prevention/plco/DQX.pdf), adapted from the Willett and Block FFQ (35, 36). The FFQ included 137 food items assessing usual diet over the past year (including 25 lycopene-containing items) and information on nutrient supplement use. Nine mutually exclusive response categories were provided for the frequency of intake. Data were retained on serving size (small, medium, and large) for 77 food items.

Nutrient intakes were derived using frequency and portion size responses from the FFQ, where nutrient values per portion were multiplied by the daily frequency of intake and summed across all relevant food items. Gram weights per portion size (small, medium, and large) were assigned using data from the two 24-hour recalls administered in the 1994 to 1996 Continuing Survey of Food Intake by Individuals, a nationally representative survey conducted during the period when the FFQ was being used (37). Cut points between small and medium and between medium and large portions correspond to the 25th and 75th percentiles for portion sizes reported by male participants ages ≥51 years in the U.S. Department of Agriculture 1994 to 1996 Continuing Survey of Food Intake by Individuals (38). Recipes for mixed dishes were used to apportion each item into constituent foods; a serving of tomatoes was defined as one half cup of tomatoes. Nutrient values from the U.S. Department of Agriculture sources (24) were supplemented with those for individual carotenoids using the University of Minnesota Nutrition Data System for Research (39) and methodology developed by Dixon et al. (40).

**Data Analysis.** Person-time was calculated from the date of the baseline prostate cancer PSA screen to the date of last contact by questionnaire, date of prostate cancer diagnosis, death, or October 1, 2001, whichever came first. During the study period, 9% of the cohort died or were lost to follow-up. Because the Prostate, Lung, Colorectal, and Ovarian Trial is an ongoing randomized clinical trial, continuing through 2015, data regarding person-years are not presented in this article. To evaluate risk for prostate cancer, we used Cox proportional hazards regression analysis, with age as the underlying time metric (41), to generate unadjusted and multivariate-adjusted relative risks (RR) and 95% confidence intervals (95% CI). We also evaluated risks for tumors of potentially greater clinical significance (stage III or IV or a Gleason score of ≥7), which, for brevity, are referred to as advanced cancer. All reported $P$s are two sided.

Some questionnaire data were missing (<1%) for six potential confounders: education, smoking status, aspirin use, physical activity, and body mass index. Sensitivity analyses under extreme assumptions did not affect results; thus, these data were imputed from group averages. Missing diabetes status (2.7%) was assigned to the no-disease category. Nonresponse to a food item was considered to indicate nonconsumption of the item.

For the analysis of risk, lycopene and total tomato servings were categorized in quintiles of average daily intake. All other tomato products had discrete intake distributions, and category cut points were chosen based on reasonable ranges in number of servings. Multivariate analyses included age (by modeling age as the underlying metric), total energy (kcal/d; quintiles), ethnicity (White, Black, Asian/Pacific Islander, other), study center, first-degree family history of prostate cancer (yes/no), current body mass index (<25, 25 to <30, ≥30), smoking status (never, current, former, pipe/cigar only), physical activity (hours spent in vigorous activity per week; none, <1, 1, 2, 3, ≥4), supplemental vitamin E intake (IU/d; 0, 0-30, >30 to 400, >400, past use), total fat intake (g/d; quintiles), red meat intake (g/d; quintiles), type II diabetes mellitus (yes/no), aspirin use (never, <1/d, ≥1/d), and total number of screening exams within the follow-up period (as a time-dependent variable). Nutrient values were adjusted for energy, using the residual method (42). Additional adjustment for calcium intake did not significantly alter results.

Tests of linear trend across increasing categories were conducted by modeling the median values of each category as a single continuous variable in the models and by

assessing significance using the Wald test (1 degree of freedom, $\chi^2$ statistic). Tests for multiplicative interaction were obtained by including a cross-product term of the dietary intake value and the risk factor variable and testing the significance using a −2 log likelihood statistic. To study whether the association between the dietary exposure and the risk of prostate cancer differed significantly between the first year and the remaining years of follow-up, we defined a time-dependent covariate, which was the product of time (dichotomized at 1 year) and the dietary exposure of interest, and tested the significance of the resulting coefficient(s) using a Wald $\chi^2$ statistic or a −2 log likelihood statistic, as appropriate.

## Results

The overall mean energy-adjusted lycopene intake was 10,904 ± 6,673 μg/d, with a 3.5-fold difference in the median lycopene values between the highest and the lowest quintile of intake. The absolute mean lycopene intake was 11,511 ± 8,498 μg/d. Food contributors to total lycopene included tomato sauce (19.3%), tomato/vegetable juice (18.8%), chili (9.2%), ketchup (6.8%), pizza (6.3%), beef stew (6.1%), canned tomatoes (5.8%), watermelon (5.6%), lasagna (5.2%), tomato/vegetable soup (5.2%), raw tomatoes (2.6%), burritos/tacos (2.3%), and smaller amounts (6.8%) from several other mixed dish items. Dietary lycopene was most strongly correlated with total tomato servings (Pearson $r = 0.78$; $P < 0.0001$), tomato juice ($r = 0.68$; $P < 0.0001$), and tomato sauce ($r = 0.44$; $P < 0.0001$).

Increased lycopene intake was associated with slightly greater physical activity, greater supplemental vitamin E use, and greater fruit, vegetable, and red meat intake (Table 1). Black men were less likely to consume high amounts of lycopene.

Among 29,361 men studied for up to 8 years (average follow-up, 4.2 years), 1,338 cases of prostate cancer (4.5%) were found, with 470 diagnosed in the first year of follow-up and 868 diagnosed thereafter. Stage and grade were confirmed for 92% of cases. The total case series included 520 cases (38.9%) with advanced disease (Gleason score ≥7 or stage III or IV). Most cases were Whites ($n$ = 1,209, 90.4%) followed by African Americans ($n$ = 88, 6.6%), Asian/Pacific Islanders ($n$ = 28, 2.1%), Hispanics ($n$ = 11, 0.8%), and American Indian/Alaskan Natives ($n$ = 2, 0.1%).

Lycopene intake was not associated with prostate cancer risk (Table 2). Reduced risks also were not found for lycopene from cooked sources consumed with fat, total tomato servings, or for most specific tomato-based foods, including several cooked products typically eaten with fat, such as spaghetti/tomato sauce, lasagna, and chili. Risks tended to decrease, however, with increasing consumption of pizza, also a cooked tomato product consumed with fat (RR, 0.83; 95% CI, 0.67-1.03 for ≥1 serving/wk versus <0.5 serving/mo; $P_{trend} = 0.06$).

For advanced prostate cancer, no associations were noted for intake of lycopene or lasagna (Table 3). Risks tended to be lower with greater consumption of spaghetti/tomato sauce (RR, 0.81; 95% CI, 0.57-1.16 for ≥2 servings/wk versus <1 serving/mo; $P_{trend} = 0.31$) and pizza (RR, 0.79; 95% CI, 0.56-1.10 for the highest group; $P_{trend} = 0.12$). When analyses were confined to high stage alone (stage III or IV, $n$ = 189 cases), risks also tended to decrease with greater consumption of spaghetti/tomato sauce (RR, 0.73; 95% CI, 0.39-1.38 for the highest group; $P_{trend} = 0.35$); however, no inverse associations were seen for any of the other variables (data not shown). In contrast to the findings for advanced prostate cancer, risk of nonadvanced prostate tended to be decreased at the highest level of lycopene intake (RR, 0.82; 95% CI, 0.64-1.05 for the highest quintile versus the lowest; $P_{trend} = 0.08$), whereas specific tomato products showed no clear association.

Similar associations were observed when examining the extreme decile rather than quintile of lycopene intake, when comparing subgroups defined by age at diagnosis or age at censor date (<65 and ≥65 years), when comparing age-only and multivariate-adjusted analyses, and with additional adjustment for fruit and vegetable intake (data not shown).

**Table 1. Decription of baseline characteristics overall and according to quintiles of energy-adjusted lycopene consumption**

| Characteristics | Quintile of lycopene consumption | | | | | Overall |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Participants ($n$) | 5,872 | 5,872 | 5,873 | 5,872 | 5,872 | 29,361 |
| Age (y) | 63.7 | 63.5 | 63.2 | 63.1 | 63.0 | 63.3 |
| Energy (kcal/d) | 2,357 | 2,328 | 2,314 | 2,354 | 2,361 | 2,342 |
| Average no. screens/y* | 0.85 | 0.83 | 0.85 | 0.85 | 0.85 | 0.85 |
| Family history of prostate cancer (%) | 7.5 | 6.9 | 7.4 | 7.2 | 7.5 | 7.3 |
| History of diabetes (%) | 7.9 | 7.9 | 7.9 | 8.6 | 10.0 | 8.5 |
| Mean current body mass index (kg/m$^2$) | 27.4 | 27.4 | 27.6 | 27.6 | 27.6 | 27.5 |
| Ever smoked (%) | 72.7 | 70.5 | 70.4 | 68.4 | 70.3 | 70.5 |
| Physical activity (hours week) | 2.0 | 2.2 | 2.2 | 2.4 | 2.4 | 2.2 |
| Race (%) | | | | | | |
| White | 86.9 | 91.2 | 91.1 | 92.5 | 91.8 | 90.7 |
| Black | 6.7 | 3.6 | 2.6 | 1.9 | 1.9 | 3.3 |
| Hispanic | 1.7 | 1.3 | 1.6 | 1.4 | 2.7 | 1.8 |
| Asian/Pacific Islander | 4.4 | 3.8 | 4.4 | 4.0 | 3.4 | 4.0 |
| American Indian/Alaskan Native | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Mean intakes | | | | | | |
| Calcium (mg/d) | 1,112 | 1,134 | 1,124 | 1,131 | 1,134 | 1,128 |
| Vitamin D (IU/d) | 443 | 445 | 439 | 446 | 449 | 444 |
| Red meat (g/d) | 85.1 | 92.1 | 97.0 | 98.7 | 94.7 | 93.5 |
| Fish (g/d) | 26.1 | 27.5 | 28.5 | 30.1 | 28.7 | 28.2 |
| Total fat (g/d) | 73.7 | 75.6 | 76.3 | 76.0 | 74.4 | 75.2 |
| Supplement vitamin E use (% ever)† | 47.8 | 50.5 | 51.3 | 53.1 | 55.4 | 51.6 |
| Fruit (servings/2000 kcal/d) | 2.7 | 2.8 | 2.9 | 3.0 | 3.2 | 2.9 |
| Vegetables (servings/2000 kcal/d) | 3.6 | 4.3 | 4.8 | 5.3 | 6.1 | 4.8 |

NOTE: All values other than age were directly standardized for age. Calcium, vitamin D, red meat, fish, and total fat intake were also standardized for energy intake. Values are mean or number of participants (%).
*Average number of prostate cancer screening examinations (PSA and/or digital rectal examination) during the period of active screening (years 0-5).
†Includes both single supplement and multivitamin use.

**Table 2. RR of prostate cancer by frequency of intake of lycopene and top food sources of lycopene**

| Nutrient/food item | Category of intake | | | | | $P_{trend}$ |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Lycopene | | | | | | |
| Quintile median (μg/d) | 5,052 | 7,555 | 9,650 | 12,271 | 17,593 | 0.33 |
| No. cases | 269 | 287 | 268 | 271 | 243 | |
| RR (95% CI)* | 1.00 | 1.10 (0.93, 1.30) | 1.06 (0.89, 1.25) | 1.07 (0.90, 1.27) | 0.95 (0.79, 1.13) | |
| Lycopene from processed sources (including fat)† | | | | | | |
| Quintile median (μg/d) | 3,009 | 4,872 | 6,438 | 8,350 | 12,647 | 0.14 |
| No. cases | 280 | 294 | 261 | 270 | 233 | |
| RR (95% CI)* | 1.00 | 1.08 (0.92, 1.27) | 0.98 (0.83, 1.17) | 1.03 (0.87, 1.22) | 0.90 (0.75, 1.08) | |
| Total tomato servings | | | | | | |
| Quintile median (serving/d) | 0.33 | 0.53 | 0.72 | 0.97 | 1.47 | 0.36 |
| No. cases | 251 | 285 | 287 | 269 | 246 | |
| RR (95% CI)* | 1.00 | 1.16 (0.97, 1.38) | 1.05 (0.87, 1.26) | 1.05 (0.87, 1.26) | 0.99 (0.81, 1.21) | |
| Raw tomatoes | | | | | | |
| Servings | <2.5/mo | 2.5/mo to 1/wk | >1/wk to 2/wk | >2/wk to 3/wk | >3/wk | 0.84 |
| No. cases | 164 | 231 | 411 | 207 | 325 | |
| RR (95% CI)* | 1.00 | 1.10 (0.90, 1.34) | 1.08 (0.90, 1.30) | 0.98 (0.80, 1.21) | 1.04 (0.86, 1.27) | |
| Canned tomatoes | | | | | | |
| Servings | <1/mo | 1-3/mo | 1/wk | ≥2/wk | | 0.50 |
| No. cases | 445 | 587 | 162 | 144 | | |
| RR (95% CI)* | 1.00 | 1.08 (0.95, 1.22) | 0.93 (0.78, 1.12) | 0.96 (0.79, 1.16) | | |
| Ketchup | | | | | | |
| Servings | <1/mo | 1-3/mo | 1-2/wk | >2/wk | | 0.68 |
| No. cases | 207 | 408 | 449 | 274 | | |
| RR (95% CI)* | 1.00 | 1.04 (0.88, 1.23) | 1.00 (0.85, 1.19) | 0.99 (0.82, 1.19) | | |
| Spaghetti/tomato sauce | | | | | | |
| Servings | <1/mo | 1-3/mo | 1/wk | ≥ 2/wk | | 0.65 |
| No. cases | 149 | 708 | 287 | 194 | | |
| RR (95% CI)* | 1.00 | 0.97 (0.81, 1.16) | 0.90 (0.73, 1.10) | 0.96 (0.76, 1.19) | | |
| Tomato and vegetable juice | | | | | | |
| Servings | <1/mo | 1-3/mo | ≥1/wk | | | 0.89 |
| No. cases | 743 | 373 | 222 | | | |
| RR (95% CI)* | 1.00 | 1.03 (0.91, 1.17) | 1.02 (0.87, 1.19) | | | |
| Pizza | | | | | | |
| Servings | <0.5/mo | 0.5-1/mo | 2-3/mo | ≥1/wk | | 0.06 |
| No. cases | 204 | 599 | 359 | 176 | | |
| RR (95% CI)* | 1.00 | 0.97 (0.82, 1.14) | 0.94 (0.78, 1.12) | 0.83 (0.67, 1.03) | | |
| Lasagna | | | | | | |
| Servings | <0.5/mo | 0.5/mo | 1/mo | >1/mo | | 0.81 |
| No. cases | 379 | 412 | 400 | 147 | | |
| RR (95% CI)* | 1.00 | 0.93 (0.81, 1.08) | 1.00 (0.86, 1.15) | 0.97 (0.79, 1.18) | | |
| Chili | | | | | | |
| Servings | <0.5/mo | 0.5/mo | 1/mo | >1/mo | | 0.38 |
| No. cases | 219 | 287 | 443 | 389 | | |
| RR (95% CI)* | 1.00 | 1.05 (0.88, 1.26) | 1.08 (0.91, 1.27) | 1.09 (0.92, 1.29) | | |

*Adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, smoking status, physical activity, supplemental vitamin E intake, total fat intake, red meat intake, history of diabetes, aspirin use, and previous number of screening exams within the follow-up period.
†Main food contributors include spaghetti sauce, chili with beans, pizza, beef stews and pies, canned tomatoes, lasagna, tomato/vegetable soup, as well as minor amounts from other food items and mixed dishes.

The hazard ratios did not vary between the first year of follow-up and the remaining observation period.

Increased lycopene consumption was associated with decreased risk for prostate cancer among men with a family history of prostate cancer (Table 4; $P_{trend} = 0.04$); risks in this group also tended to decrease in relation to consumption of specific tomato-based foods commonly eaten with fat. No such associations were noted among men who reported a negative history of prostate cancer in their families.

## Discussion

In this large prospective study, we found no overall association between prostate cancer risk and dietary intake of either lycopene or total tomato products. Although not statistically significant, inverse trends were found with pizza consumption, for all prostate cancer; with lycopene, for nonadvanced cancer; and with pizza and spaghetti sauce, for advanced disease. We also noted that lycopene and pizza were inversely associated with risk among those with a family history of prostate cancer.

Results from a recent meta-analysis of 11 case-control studies and 10 cohort studies indicated that serum lycopene (RR, 0.74; 95% CI, 0.59-0.92 for the high versus low levels) was associated with a greater reduction in prostate cancer risk than dietary lycopene (RR, 0.89; 95% CI, 0.81-0.98 for the high versus low intake), whereas cooked tomato products (RR, 0.81; 95% CI, 0.71-0.92 for high versus low intake) were associated with greater risk reduction than raw tomato products (RR, 0.89; 95% CI, 0.80-1.00 for high versus low intake), although reductions in risk were modest in all instances (23). Results from the meta-analysis were not stratified by degree of disease progression; however, others suggest that high serum lycopene is inversely associated, in particular, with risk of aggressive prostate cancer (4, 11, 13).

The weak inverse association noted in the meta-analysis with increased dietary lycopene was driven largely by data from the Health Professionals' Follow-up Study (RR, 0.84; 95% CI, 0.73-0.96; ref. 4). Data on plasma lycopene from this cohort

(published subsequent to the meta-analysis) do not indicate an association with prostate cancer risk overall (43). In contrast to our subgroup findings for dietary lycopene, the Health Professionals' Follow-up Study cohort found an inverse association for plasma lycopene among participants ages ≥65 years and those without a family history of prostate cancer (43), and a stronger inverse association for dietary lycopene among men ages ≥65 years (4).

Findings from three prospective studies yielded conflicting results with respect to raw tomato intake, with two finding a significant inverse association for high raw tomato intake (refs. 3, 44; RR, 0.57 and 0.74, respectively) and the third finding no overall association (RR, 1.00 per 25 g increase; ref. 14). In the Health Professionals' Follow-up Study cohort, processed tomato products (e.g., spaghetti sauce; ref. 4) and pizza (44) were evaluated showing strong inverse associations; certain risk estimates seemed to be more pronounced for advanced prostate cancer (4, 44). Our study is the only other prospective evaluation of processed tomato products and does not provide strong corroboration; however, case-control studies have indicated cooked tomato products as generally stronger predictors of reduced risk (7-9).

Tomato products consumed in oil, such as pizza (7.5 g fat per serving), spaghetti/tomato sauce (14.6 g), and lasagna (23.8 g), are particularly bioavailable lycopene sources, due to greater intestinal absorption in association with fat. With the exception of chili, which is also typically high in fat (16.5 g/serving), none of the other main contributors to tomato intake assessed in our study had comparable amounts of fat (range, 0.16-4.7 g/serving).

Heating processes enhance lycopene bioavailability by rupture of plant cell walls (30, 45) and transformation from the *trans*- to *cis*-isomer, which is more readily absorbed in the gut (27, 45-47). Lycopene in fresh tomatoes occurs almost entirely in the *trans*-form. In the prostate, 80% to 90% of lycopene is in the *cis*-form (48). Yet, our study found only weak relationships between oil content or cooking of tomato products and prostate cancer risk.

Lycopene may protect prostate tissue from oxidative DNA damage by limiting cellular free radical exposure (49); however, tomatoes and tomato products also contain other carotenoids and phytochemicals (50), which may confer protection (51, 52). In an experimental feeding study (53), rats fed whole tomato powder were less likely to die from prostate cancer compared with rats fed synthetic lycopene, perhaps implicating other active components of tomatoes.

Our findings of protective effects of lycopene and certain tomato-based products in subanalyses are based on small numbers and may be due to chance. Genetic underpinnings of prostate cancer are only beginning to be understood, and there may be inter-relationships between genetic polymorphisms in metabolism-related genes and a strong antioxidant, such as lycopene in the diet. For example, a polymorphism in *MnSOD*, a gene that protects cells from oxidative damage, potentially modifies risk of prostate cancer in relation to serum lycopene (54). Further research is needed to determine whether this gene, or others, are associated with familial prostate cancer and to corroborate whether certain polymorphisms alter the effect of antioxidant intake on prostate cancer risk.

A strength of our study is the detailed assessment of >25 individual food items related to tomato product intake, with attention to recipes and portion sizes, allowing us to assess risk according to multiple sources of lycopene. For example, we distinguish between canned (a processed source) and fresh tomatoes (unprocessed) and queried as to ketchup, pizza, lasagna, chili, and beef stew consumption, likely reducing misclassification of lycopene intake. Due in part to this detailed assessment and the use of nutrient data from the revised U.S. Department of Agriculture/NCC Carotenoid Database (updated in 1999) and the University of Minnesota Nutrition

**Table 3. RR of prostate cancer by lycopene and tomato product consumption according to degree of disease progression at diagnosis**

| | Advanced prostate cancer* | | Nonadvanced prostate cancer† | |
|---|---|---|---|---|
| | No. cases | RR (95% CI)‡ | No. cases | RR (95% CI)‡ |
| Lycopene | | | | |
| Q1 | 101 | 1.00 | 148 | 1.00 |
| Q2 | 121 | 1.25 (0.96, 1.63) | 144 | 0.99 (0.78, 1.25) |
| Q3 | 91 | 0.98 (0.74, 1.31) | 160 | 1.13 (0.90, 1.41) |
| Q4 | 103 | 1.11 (0.84, 1.47) | 144 | 1.01 (0.80, 1.27) |
| Q5 | 104 | 1.11 (0.83, 1.47) | 118 | 0.82 (0.64, 1.05) |
| $P_{trend}$ | | 0.80 | | 0.08 |
| Spaghetti/tomato sauce | | | | |
| <1/mo | 65 | 1.00 | 74 | 1.00 |
| 1-3/mo | 274 | 0.88 (0.67, 1.16) | 379 | 1.03 (0.80, 1.33) |
| 1/wk | 112 | 0.84 (0.61, 1.15) | 157 | 0.96 (0.72, 1.28) |
| ≥2/wk | 69 | 0.81 (0.57, 1.16) | 104 | 0.99 (0.73, 1.35) |
| $P_{trend}$ | | 0.31 | | 0.77 |
| Pizza | | | | |
| <0.5/mo | 86 | 1.00 | 99 | 1.00 |
| 0.5-1/mo | 235 | 0.89 (0.69, 1.15) | 316 | 1.06 (0.84, 1.34) |
| 2-3/mo | 128 | 0.78 (0.59, 1.05) | 204 | 1.09 (0.85, 1.41) |
| ≥1/wk | 71 | 0.79 (0.56, 1.10) | 95 | 0.90 (0.67, 1.22) |
| $P_{trend}$ | | 0.12 | | 0.42 |
| Lasagna | | | | |
| <0.5/mo | 145 | 1.00 | 203 | 1.00 |
| 0.5/mo | 158 | 0.94 (0.74, 1.18) | 227 | 0.95 (0.78, 1.16) |
| 1/mo | 162 | 1.08 (0.86, 1.36) | 202 | 0.90 (0.73, 1.10) |
| >1/mo | 55 | 0.96 (0.70, 1.33) | 82 | 0.94 (0.72, 1.23) |
| $P_{trend}$ | | 0.92 | | 0.66 |

NOTE: Advanced/nonadvanced status was undetermined for 104 cases.
*Advanced cases defined as Gleason score of ≥7 or stage III or IV ($n$ = 520).
†Nonadvanced cases defined as Gleason score <7 and stage I or II ($n$ = 714).
‡Adjusted for age, total energy, race, study center, family history of prostate cancer, body mass index, smoking status, physical activity, supplemental vitamin E intake, total fat intake, red meat intake, history of diabetes, aspirin use, and previous number of screening exams within the follow-up period.

**Table 4. RR of prostate cancer by lycopene and tomato product consumption according to family history of prostate cancer**

| | Family history of prostate cancer | | No family history of prostate cancer | |
|---|---|---|---|---|
| | No. cases | RR (95% CI)* | No. cases | RR (95% CI)* |
| Lycopene | | | | |
| Q1 | 38 | 1.00 | 231 | 1.00 |
| Q2 | 34 | 0.92 (0.57, 1.49) | 253 | 1.12 (0.94, 1.34) |
| Q3 | 23 | 0.59 (0.35, 1.01) | 245 | 1.13 (0.94, 1.36) |
| Q4 | 21 | 0.53 (0.30, 0.93) | 250 | 1.15 (0.96, 1.39) |
| Q5 | 25 | 0.62 (0.37, 1.06) | 218 | 1.01 (0.83, 1.22) |
| $P_{trend}$ | | 0.04 | | 0.78 |
| $P_{interaction}$ = 0.22 | | | | |
| Spaghetti/tomato sauce | | | | |
| <1/mo | 14 | 1.00 | 135 | 1.00 |
| 1-3/mo | 81 | 1.27 (0.71, 2.27) | 627 | 0.94 (0.78, 1.14) |
| 1/wk | 33 | 1.15 (0.60, 2.21) | 254 | 0.88 (0.71, 1.09) |
| ≥2/wk | 13 | 0.68 (0.31, 1.51) | 181 | 0.99 (0.79, 1.25) |
| $P_{trend}$ | | 0.12 | | 0.88 |
| $P_{interaction}$ = 0.08 | | | | |
| Pizza | | | | |
| <0.5/mo | 24 | 1.00 | 180 | 1.00 |
| 0.5-1/mo | 63 | 0.81 (0.50, 1.32) | 536 | 0.99 (0.83, 1.18) |
| 2-3/mo | 38 | 0.78 (0.45, 1.33) | 321 | 0.96 (0.79, 1.16) |
| ≥1/wk | 16 | 0.58 (0.30, 1.14) | 160 | 0.86 (0.68, 1.08) |
| $P_{trend}$ | | 0.15 | | 0.12 |
| $P_{interaction}$ = 0.61 | | | | |
| Lasagna | | | | |
| <0.5/mo | 44 | 1.00 | 335 | 1.00 |
| 0.5/mo | 49 | 1.02 (0.66, 1.57) | 363 | 0.93 (0.80, 1.09) |
| 1/mo | 42 | 0.86 (0.55, 1.34) | 358 | 1.00 (0.86, 1.17) |
| >1/mo | 6 | 0.38 (0.16, 0.91) | 141 | 1.00 (0.82, 1.24) |
| $P_{trend}$ | | 0.02 | | 0.68 |
| $P_{interaction}$ = 0.03 | | | | |

NOTE: $n$ = 2,145 men with a positive family history of prostate cancer (one or more first-degree relatives), including 141 cases.
*Adjusted for age, total energy, ethnic origin, study center, body mass index, smoking status, physical activity, supplemental vitamin E intake, total fat intake, red meat intake, history of diabetes, aspirin use, and previous number of screening exams within the follow-up period.

Data System for Research (40), we report higher lycopene levels than other epidemiologic studies. This is, however, a one-time dietary assessment, and there are no direct data to indicate that our approach results in improved validity compared with briefer data collection instruments used in other studies. Although dietary intake may offer the advantage of characterizing long-term intake, it generally correlates poorly with serum lycopene (31), which better reflects short-term lycopene absorption, metabolism, and bioavailability. Consideration must therefore be given to the possibility of attenuated risk estimates due to random error in quantifying and/or capturing the most relevant measure of intake.

Carried out in the screening arm of a randomized control trial to evaluate PSA and digital rectal examination as prostate cancer screening modalities, most of the prostate cancer cases in our study were screen detected. We assessed the potential for detection bias by creating a time-dependent variable representing total number of prostate screening exams. In this way, at any given time point, only participants who had had the same number of screening exams (assessed since baseline) and thus the same opportunity for cancer detection were being compared. By virtue of the study design, we largely avoid differential misclassification resulting from an inability to distinguish between diagnostic screening, done in response to signs or symptoms, and true screening (55), as well as any bias that could result from men with healthier diets seeking prostate screening examinations. Although we were able to account for any differences in number of previous PSA tests, it is reassuring that results were not confounded by exclusion of the screening variable from the model.

Prostate cancers found through PSA testing may have different biological characteristics and associated etiologic profiles. To address this, we carried out analyses by disease subgroup. Our results do not differ substantively for advanced versus nonadvanced cases, although greater lycopene intake was weakly, nonsignificantly associated with reduced risk in nonadvanced cases. We also examined stage- and grade-specific associations, but no clear patterns were found (data not shown).

The possibility of uncontrolled confounding cannot be excluded, but the multivariate analyses were virtually identical to the simple age-adjusted analyses. In addition, tomato products were not strongly associated with dietary and lifestyle factors (Table 1) other than fruit, vegetable, red meat, and supplemental vitamin E use, and adjustment for these variables did not alter the results. We conducted a sensitivity analysis, verifying that exclusion of cases diagnosed within a year after the baseline screening who may have had underlying yet insidious disease at baseline did not materially alter the observed associations.

The apparent protective effects that we observed were neither strong nor consistent and do not provide compelling evidence that lycopene or tomato products in various forms protects from prostate cancer. Cooking process and concurrent consumption of fat might be necessary for the putative benefits of tomato products to be realized, however, increased lycopene or tomato product intake is unlikely, in itself, to represent a substantive preventive measure for prostate cancer.

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# A Prospective Study of Lycopene and Tomato Product Intake and Risk of Prostate Cancer

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