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ARTICLE

Dietary Lycopene, Angiogenesis, and Prostate Cancer: A Prospective Study in the Prostate-Specific Antigen Era

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Background The role of lycopene in prostate cancer prevention remains controversial. We examined the associations between dietary lycopene intake and prostate cancer, paying particular attention to the influence of prostate-specific antigen screening, and evaluated tissue biomarkers in prostate cancers in relation to lycopene intake.

Methods Among 49 898 male health professionals, we obtained dietary information through questionnaires and ascertained total and lethal prostate cancer cases from 1986 through January 31, 2010. Cox regression was used to estimate multivariable hazard ratios (HRs) and 95% confidence intervals (CIs). Tissue microarrays and immunohistochemistry were used to assess tumor biomarker expression in a subset of men. Two-sided χ^2 tests were used to calculate the *P* values.

Results Higher lycopene intake was inversely associated with total prostate cancer and more strongly with lethal prostate cancer (top vs bottom quintile: HR = 0.72; 95% CI = 0.56 to 0.94; P_{trend} = .04). In a restricted population of screened participants, the inverse associations became markedly stronger (for lethal prostate cancer: HR = 0.47; 95% CI = 0.29 to 0.75; P_{trend} = .009). Comparing different measures of dietary lycopene, early intake, but not recent intake, was inversely associated with prostate cancer. Higher lycopene intake was associated with biomarkers in the cancer indicative of less angiogenic potential.

Conclusions Dietary intake of lycopene was associated with reduced risk of lethal prostate cancer and with a lesser degree of angiogenesis in the tumor. Because angiogenesis is a strong progression factor, an endpoint of lethal prostate cancer may be more relevant than an endpoint of indolent prostate cancer for lycopene in the era of highly prevalent prostate-specific antigen screening.

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In spite of recent controversy regarding prostate cancer screening, overdiagnosis, and excessive therapy, prostate cancer remains the second leading cause of cancer mortality in American men, accounting for more than 30 000 deaths (1).

Human prostatic cancer lesions can arise in middle age and often remain latent years before the development of any symptoms (2). Before the widespread use of the prostate-specific antigen (PSA) test for screening, most of the cancers diagnosed were palpable or caused symptoms and were usually detected at more-advanced stages. However, most cancers diagnosed in the PSA era are found at localized stages, are asymptomatic and biologically indolent, and would have remained undiagnosed in the pre-PSA era. Because risk factors for prostate cancer may differ by subtype of cancer and may act at different stages of the disease (3), epidemiological studies of prostate cancer conducted in different settings may produce different results.

Lycopene, a carotenoid with multiple bioactivities, is found abundantly in tomato, tomato-based products, pink grapefruit, and watermelon (4). A number of studies have investigated lycopene, or lycopene-rich food such as tomato and tomato-based products, in relation to prostate cancer risk (5–25). In a meta-analysis of studies published up to 2003 (26), high intakes of tomato or tomato-based products was associated with a 10% to 20% reduction in prostate cancer risk, and high serum or plasma concentrations of lycopene were associated with a 25% reduced risk. Among recent studies of lycopene and prostate cancer, some support an inverse association (18,19,27,28), whereas others present null findings (8,9,17,20,22,29). The heterogeneity of prostate cancers diagnosed in the PSA era may contribute to this inconsistency.

Previously, we reported that dietary intake of lycopene was associated with a 20% lower risk incident of prostate cancer in a prospective study of health professionals (5). This inverse association persisted in an updated 2002 analysis (10). In the same population, high level of lycopene in the plasma was associated with a non-statistically significant 34% reduction in risk of overall prostate cancer (27).

In this study, we aimed to reassess the association between prostate cancer and lycopene intake based on dietary data from

1986 to 2006 and follow-up through 2010 within this same cohort, focusing on four specific aims. First, in addition to total cancer incidence, we investigated the lycopene intake in relation to risk of lethal prostate cancer. Second, we identified a restricted population of participants who had been initially screened negative by PSA testing at baseline to better assess the association of lycopene with incident prostate cancer in contrast with indolent prevalent prostate cancers discovered during the early part of the PSA era with initial screening tests. Third, because multiple dietary assessments of lycopene intake were available, we examined whether diet at different time periods influenced the results. Finally, to identify the potential anticancer mechanism of lycopene, we evaluated tumor tissue biomarkers of angiogenesis, apoptosis, and cell proliferation and differentiation in relation to lycopene intake.

Methods

Study Population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study that consists of 51 529 US male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, veterinarians) aged between 40 and 75 years at baseline in 1986. The men were followed through questionnaires every 2 years to obtain information on lifestyle factors and health outcomes. A food frequency questionnaire (FFQ) was mailed to assess usual diet every 4 years. Participants who were diagnosed with cancer before 1986, those without a completed FFQ at baseline, those who reported implausibly high (>4200 calories) or low (<800 calories) energy intake, or those who had left more than 70 items blank on the FFQ were excluded from the baseline cohort. The HPFS is approved by the Human Subjects Committee at the Harvard School of Public Health, and written informed consents were provided by all participants.

Assessment of Dietary Intake

Dietary intake was assessed by self-administered semiquantitative FFQ in 1986, 1990, 1994, 1998, 2002, and 2006. The FFQ contains a list of 131 food and beverage items for which commonly used units or portion sizes are specified. The participants were asked to report how often, on average, in the previous year, they consumed each food item. Nutrient intakes were then calculated by multiplying the frequency of consuming a certain food or beverage item by the nutrient content of that serving and then summing contributions from all food and beverage items using composition values from US Department of Agriculture (USDA) sources supplemented with other data. Carotenoid values in our nutrient database were updated using the USDA–National Cancer Institute database (30,31). The carotenoid content of tomato-based products was further updated with values from the USDA, which were determined through reversed-phase high-performance liquid chromatography (32). In the 1986 FFQ, food sources for lycopene included tomato, tomato sauce, tomato juice, pizza, watermelon, and pink grapefruit. The subsequent FFQs have also included salsa, picante or taco sauce, and ketchup or red chili sauce. Among men for whom blood sample measurement of lycopene was available (n = 1200), the mean plasma lycopene levels were 681.7, 761.6, 820.0, 884.8, and 934.5 mol/L for the lowest to the highest quintile of dietary lycopene intake, respectively.

Ascertainment and Classification of Prostate Cancer

Prostate cancer diagnoses were initially identified through self-report by the participants or their next of kin on the biennial questionnaire, then confirmed by review of medical records and pathology reports. Clinical information, such as tumor stage and PSA at diagnosis and Gleason score, was acquired through a standardized review of medical records. Deaths were ascertained through repeated mailings, telephone calls to nonrespondents, and searches of the National Death Index. All causes of death were confirmed by extensive review of death certificates and medical records. Follow-up rates for cancer and for mortality were greater than 96% and nearly 100%, respectively. Participants who had prostate cancer were separately followed through an annual prostate cancer–specific questionnaire. Detailed information on treatment and development of metastasis was obtained by questionnaires and collection of medical records.

In this study, we considered total prostate cancer as all incident cases during the follow-up excluding stage T1a cancers, which are discovered incidentally during treatment for benign prostatic hypertrophy. Lethal prostate cancers were defined as cancers that caused death or distant metastases before the end of follow-up. Organ-confined prostate tumors are those that were confined within prostate gland or had limited extraprostatic extension (stage T1b, T1c, T2, T3a and N0 or Nx and M0 at diagnosis) (33). Through 2010, there were 5728 total incident prostate cancers and 658 lethal prostate cancers.

Archival formalin-fixed, paraffin-embedded tumor specimens have been retrieved for a subset of men with clinically localized prostate cancer diagnosed through 2002 (n = 1180) who underwent prostatectomy (95%) and transurethral resection of the prostate (5%), as previously described (34,35).

Immunohistochemistry

Angiogenesis. Evaluation of angiogenic biomarkers has been described in detail previously (34). Briefly, protein expression of endothelial cell marker CD34 was ascertained on 5-micron sections. The size and architecture of microvessels were quantified by semi-automated image analysis using Image ProPlus 4.5 software (Media Cybernetics, Rockville, MD). Vessel size was determined as the average area comprised by a vessel (μm^2). The irregularity of the vessel lumen was calculated by perimeter^2/4 × Π × area, with a value of 1.0 indicating a perfect circle and values greater than 1.0 indicating increasing irregularity.

Tissue Microarrays. The construction and the immunohistochemical staining of tissue microarrays have been described previously (36,37). Briefly, high-density tumor tissue microarrays were constructed by sampling 0.6-mm paraffin-embedded tumor tissue cores (at least three cores per subject) from men with localized prostate cancer. Our pathologists (M. Loda, M. Fiorentino, S. Finn, R. Flavin) reviewed hematoxylin and eosin slides to confirm prostate cancer and to provide uniform Gleason grading.

Apoptosis. The TUNEL assay was performed on 5-micron sections of the tumor tissue microarrays to identify the percentage of tumor

cells undergoing apoptosis. The procedure was carried out using the Apoptag Peroxidase In situ kit (Chemicon International, Temecula, CA) according to the manufacturer's instructions. The entire area of each tumor core was evaluated. Apoptosis was quantified as the percentage of positively stained area over the whole tumor area.

Proliferation. The expression of Ki-67, a cell proliferation marker, was assessed on 5-micron sections of the tumor tissue microarrays using a rabbit polyclonal antiboday (Vector Labs, Burlingame, CA; diluted 1:1500). After immunohistochemical staining, the tumor areas of each core were selected for quantitative image analysis using the Ariol instrument SL-50 (Applied Imaging, San Jose, CA). Cell proliferation was quantified as the percentage of Ki-67–positive nuclei over all tumor nuclei.

Statistical analysis

For the analyses of total incident prostate cancer, we calculated each individual's person-time from date of return of the baseline questionnaire to the date of prostate cancer diagnosis, date of death from any cause, or the end of follow-up (January 31, 2010), whichever came first. For the analyses of lethal prostate cancer, we calculated each individual's person-time from date of return of the baseline questionnaire to the date of metastasis or date of death or the end of follow-up. We excluded participants with history of cancer or with missing data on dietary intake of lycopene at baseline in 1986. For men who were diagnosed with prostate cancer, we only considered their diet before cancer diagnosis. Because approximately 90% of the HPFS participants are white, we did not perform stratified analyses by ethnicity.

All variables for dietary intake were energy adjusted using the residual method (38). To reduce intra-individual variation and represent long-term intake, we calculated cumulative updated average of lycopene intake as the primary measure of exposure. For example, the lycopene intake reported by the participants in 1986 was used to compute exposure in the 1986 to 1990 follow-up period, the average of lycopene intakes reported in 1986 and 1990 was used to compute exposure in the 1990 to 1994 follow-up period, and so on. We also used baseline lycopene intake (1986) and simply updated lycopene intake (most recent intake) as alternative measures of exposure. Variables of lycopene intakes were categorized into quintiles based on the total study population.

We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for total and lethal prostate cancer. Models were stratified by year of questionnaire return and age at baseline (in months) and were adjusted for potential confounders that have been previously identified as risk factors of prostate cancer in this cohort. Interaction terms for lycopene intakes and age and year of questionnaire return were added into the models to test for the assumption of proportional hazards. Covariates included body mass index (BMI), height, family history of prostate cancer, race/ethnicity, smoking, vigorous physical activity, total energy, alpha-linolenic acid, calcium, and coffee. BMI, smoking, and vigorous physical activity were updated in each questionnaire circle, whereas cumulative updated average of intakes were used for total energy, alpha-linolenic acid, calcium, and coffee. To test for a linear trend across categories of intake, we modeled lycopene intake as a continuous variable using the median intake for each category.

To investigate whether PSA screening influenced the association between lycopene intake and prostate cancer incidence, we performed stratified survival analyses by time periods before and after the clinical introduction of PSA test in 1994.

To reduce the influence of PSA screening as a potential confounder of the relation between lycopene and total and lethal prostate cancer, we restricted in secondary analysis the study population to the participants who reported at least one negative PSA test by 2008. The follow-up for these participants started in 1994, when we first asked about PSA screening in the questionnaires, or in the year when their PSA testing was first reported. We then repeated the survival analyses to evaluate the associations between cumulative updated average of lycopene intake and subgroups of prostate cancer. To investigate whether the timing of diet had an effect on the association, we repeated the analyses using baseline or simply updated lycopene intake. We also put any two measures (for example, baseline and simply updated intake) simultaneously in the Cox regression models to explore the potentially different associations according to timing of the lycopene intake.

To gain insight into potential mechanisms as to how lycopene may affect prostate cancer progression, we evaluated levels of tissue biomarkers in the tumor specimen across the quintile of lycopene intake. These markers include characteristics of angiogenesis such as microvessel size and irregularity, apoptosis, and cell proliferation and differentiation. In addition to individual angiogenic markers, we also generated an angiogenic score based on microvessel density, diameter, area, and irregularity using factor analysis. This score has a mean of zero, and lower score reflects a greater angiogenic potential. We calculated a *P* value from analysis of variance for these markers across lycopene intake quintiles. To minimize the influence of tumor stage, we repeated the evaluation of angiogenic markers in tumors that were organ confined or with limited extraprostatic extension at prostatectomy (pT1–pT3a, N0, M0). We previously showed that among the markers of angiogenesis, vessel irregularity was the angiogenic feature most strongly predicting lethal prostate cancer (34), and therefore the association with this marker was our primary hypothesis.

All statistical analyses were two-sided and a *P* value of less than .05 was considered statistically significant. We conducted all analyses using the SAS software version 9.1 (SAS Institute, Cary, NC).

Results

Baseline height, BMI, family history of prostate cancer, smoking status, dietary intakes of total energy, carbohydrates, protein, alpha-linolenic acid, and calcium, and percentage of PSA screening by the year 2008, did not vary remarkably across quintiles of baseline lycopene intake (Table 1). Participants in the upper quintiles of lycopene intake were slightly younger and more likely to engage in vigorous physical activity. Men who consumed more lycopene in their diet also consumed less alcohol, coffee, and all three types of fats and slightly more fruits, vegetables, and dietary fiber. Dietary intake of lycopene was positively correlated with consumption of tomato and tomato products, such as tomato juice, tomato sauce, and pizza.

We found statistically significant inverse associations between quintiles of lycopene intake and incidence of total prostate cancer (P_{trend} = .009), as well as lethal prostate cancer (P_{trend} = .04)

Table 1. Lifestyle characteristics (at baseline unless otherwise indicated) according to the quintiles (Q) of dietary lycopene intake in the Health Professionals Follow-up Study cohort*

	Dietary lycopene intake, energy-adjusted (μg/day)				
	Q1	Q2	Q3	Q4	Q5
Characteristics	**0–3687**	**3688–5301**	**5302–7062**	**7063–10 130**	**10 131–115 012**
No. of men	9470	9609	9595	9598	9626
Age, y	56.8 (9.8)	54.2 (9.7)	53.2 (9.5)	52.8 (9.6)	52.9 (9.6)
Height, in	70.2 (2.6)	70.2 (2.6)	70.2 (2.7)	70.1 (2.7)	70.0 (2.7)
BMI, kg/m^2	25.4 (3.5)	25.4 (3.2)	25.5 (3.3)	25.6 (3.3)	25.8 (3.6)
White, %	89.7	91.0	91.1	91.4	90.8
Family history of prostate cancer, %	11.7	11.3	11.0	10.7	10.0
Smoking status, %					
Never smoker	43.8	44.8	44.1	46.1	44.2
Past smoker, quit ≤10 y	13.3	12.6	12.8	12.7	12.8
Past smoker, quit >10 y	27.4	28.7	29.6	28.8	30.4
Current smoker	11.9	9.9	9.5	8.4	8.6
Missing	3.6	4.0	4.0	4.1	4.0
Vigorous physical activity ≥10.5 METs/week, %	28.7	31.0	34.3	36.2	37.7
Ever PSA screening, %	87.5	88.8	88.6	89.3	88.2
Dietary intake of					
Total calories, kcal/day	2058 (673)	2071 (597)	1951 (566)	1903 (632)	1949 (615)
Carbohydrates, g/day	235 (91)	240 (83)	229 (79)	226 (86)	236 (87)
Protein, g/day	93.4 (33.8)	94.0 (29.4)	89.9 (28.0)	88.6 (30.3)	91.7 (31.1)
Dietary fiber, g/day	20.5 (9.2)	21.9 (8.6)	21.6 (8.6)	22.0 (9.1)	23.7 (10.0)
Total saturated fat, g/day	26.6 (12.2)	26.1 (10.5)	23.9 (9.4)	22.8 (10.1)	22.3 (9.8)
Total monounsaturated fat, g/day	29.4 (13.1)	29.0 (11.2)	26.6 (10.1)	25.4 (10.8)	25.3 (10.6)
Total polyunsaturated fat, g/day	13.6 (6.5)	13.7 (5.6)	12.8 (5.1)	12.6 (5.3)	12.8 (5.1)
Total fruits, serving/day	2.1 (1.5)	2.3 (1.5)	2.4 (1.5)	2.5 (1.6)	2.7 (1.8)
Total vegetables, serving/day	2.3 (1.4)	2.8 (1.4)	3.0 (1.5)	3.3 (1.7)	4.0 (2.0)
Tomatoes, serving/week	1.4 (1.4)	2.2 (1.8)	2.7 (2.0)	3.2 (2.3)	3.9 (2.9)
Tomato juice, serving/week	0.1 (0.3)	0.2 (0.4)	0.3 (0.4)	0.6 (0.8)	1.5 (2.3)
Tomato sauce, serving/week	0.3 (0.4)	0.6 (0.3)	0.7 (0.4)	1.0 (0.8)	2.2 (1.7)
Pizza, serving (2 slices)/week	0.3 (0.3)	0.5 (0.4)	0.6 (0.5)	0.7 (0.7)	0.9 (1.0)
Alcohol, g/day	12.4 (17.8)	11.9 (15.9)	11.2 (14.7)	10.4 (14.0)	10.7 (14.5)
α-Linolenic acid, g/day	1.0 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)
Calcium, mg/day	910 (462)	900 (417)	894 (409)	894 (420)	889 (420)
Coffee, cup/day	1.5 (1.8)	1.4 (1.7)	1.3 (1.6)	1.2 (1.5)	1.2 (1.5)

* Values are means (SD) or percentages and are standardized to the age distribution of the study population. BMI = body mass index; PSA = prostate-specific antigen.

(Table 2). Compared with the bottom quintile, the top quintile of lycopene intake was associated with a hazard ratio of 0.91 (95% CI = 0.84 to 1.00) for total prostate cancer and a hazard ratio of 0.72 (95% CI = 0.56 to 0.94) for lethal prostate cancer. In the time period before the widespread use of PSA screening (before 1994), there was a borderline significant inverse association between lycopene intake and total prostate cancer (top quintile vs bottom quintile: HR = 0.85; 95% CI = 0.72 to 1.00; P_{trend} = .07). However, during that period, men in the top quintile were at a 27.7% lower risk for lethal prostate cancer (HR = 0.72; 95% CI = 0.51 to 1.00; P_{trend} = .07) compared with those in the bottom quintile of lycopene intake. In the PSA era, comparing participants in the top quintile with those in the bottom quintile of lycopene intake, there was a slight reduction in incidence of total prostate cancer, but this was less than that in the pre-PSA era. Only the lower risk for lethal prostate cancer remained unchanged (top quintile vs bottom quintile: HR = 0.72; 95% CI = 0.49 to 1.10; P_{trend} = .10).

To further reduce the influence of PSA screening on the observed association, in a subanalysis we restricted the study population to men who had at least one negative PSA test. In addition to cumulative updated average of lycopene intake, we also evaluated baseline and simply updated lycopene intake as alternative measures of exposure. Because the results from the age-adjusted analyses were similar to those from full multivariable models, we only present the multivariable hazard ratios (Table 3). Results from the multivariable models adjusting for various dietary factors were comparable with those from the models without adjusting for them. The strongest associations were observed for lethal prostate cancer with baseline or cumulative updated average of lycopene intake (top quintile vs bottom quintile: HR = 0.48, 95% CI = 0.30 to 0.78, P_{trend} = .009 for baseline lycopene intake; HR = 0.47, 95% CI = 0.29 to 0.75, P_{trend} = .009 for cumulative updated lycopene intake). Men with the highest intake were half as likely to develop lethal prostate cancer compared with those with the lowest intake. The association was much weaker for the simply updated diet, reflecting most recent intake, suggesting that lycopene may be acting early in the disease process.

To evaluate which measure of exposure best captures the protective association with lycopene, we put any two measures simultaneously in the Cox regression models (Table 4). The multivariable

Table 2. Hazard ratios (HRs) and 95% confidence interval (CIs) of total and lethal prostate cancer in relation to lycopene intake in the Health Professionals Follow-up Study (1986–January, 2010) cohort

	Cumulative updated average of dietary lycopene intake, HR (95% CI)					
Prostate cancer and time period	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}*
Total prostate cancer	1209	1236	1144	1102	1037	
Adjusted for age	1.00 (referent)	1.10 (1.00 to 1.20)	1.00 (0.95 to 1.10)	1.00 (0.94 to 1.10)	0.96 (0.88 to 1.00)	.07
Multivariable adjusted†	1.00 (referent)	1.00 (0.96 to 1.10)	0.97 (0.90 to 1.10)	0.97 (0.89 to 1.10)	0.93 (0.86 to 1.00)	.03
Multivariable adjusted‡	1.00 (referent)	1.00 (0.95 to 1.10)	0.96 (0.89 to 1.00)	0.96 (0.88 to 1.00)	0.91 (0.84 to 1.00)	.009
Lethal prostate cancer	184	136	118	128	92	
Adjusted for age	1.00 (referent)	0.92 (0.74 to 1.10)	0.86 (0.68 to 1.10)	0.98 (0.78 to 1.20)	0.72 (0.56 to 0.92)	.02
Multivariable adjusted†	1.00 (referent)	0.91 (0.73 to 1.10)	0.85 (0.68 to 1.10)	1.00 (0.81 to 1.30)	0.75 (0.58 to 0.97)	.08
Multivariable adjusted‡	1.00 (referent)	0.90 (0.72 to 1.10)	0.84 (0.66 to 1.10)	0.99 (0.78 to 1.20)	0.72 (0.56 to 0.94)	.04
Pre–prostate-specific antigen era						
Total prostate cancer	420	310	280	262	241	
Adjusted for age	1.00 (referent)	0.92 (0.79 to 1.10)	0.92 (0.79 to 1.10)	0.93 (0.80 to 1.10)	0.85 (0.72 to 0.99)	.06
Multivariable adjusted†	1.00 (referent)	0.93 (0.80 to 1.10)	0.91 (0.78 to 1.10)	0.95 (0.81 to 1.10)	0.87 (0.74 to 1.00)	.10
Multivariable adjusted‡	1.00 (referent)	0.92 (0.79 to 1.10)	0.90 (0.77 to 1.00)	0.93 (0.80 to 1.10)	0.85 (0.72 to 1.00)	.07
Lethal prostate cancer	104	73	63	72	48	
Adjusted for age	1.00 (referent)	0.93 (0.69 to 1.30)	0.86 (0.63 to 1.20)	1.10 (0.79 to 1.4)	0.71 (0.50 to 1.00)	.10
Multivariable adjusted†	1.00 (referent)	0.93 (0.69 to 1.30)	0.89 (0.65 to 1.20)	1.10 (0.84 to 1.5)	0.76 (0.54 to 1.10)	.30
Multivariable adjusted‡	1.00 (referent)	0.93 (0.68 to 1.30)	0.88 (0.64 to 1.20)	1.10 (0.81 to 1.5)	0.72 (0.51 to 1.00)	.20
Prostate-specific antigen era						
Total prostate cancer	789	926	864	840	796	
Adjusted for age	1.00 (referent)	1.20 (1.10 to 1.30)	1.10 (0.99 to 1.20)	1.10 (0.97 to 1.20)	1.00 (0.91 to 1.10)	.30
Multivariable adjusted†	1.00 (referent)	1.10 (0.99 to 1.20)	1.00 (0.91 to 1.10)	0.99 (0.89 to 1.10)	0.96 (0.87 to 1.10)	.09
Multivariable adjusted‡	1.00 (referent)	1.10 (0.98 to 1.20)	1.00 (0.90 to 1.10)	0.98 (0.89 to 1.10)	0.95 (0.86 to 1.10)	.05
Lethal prostate cancer	80	63	55	56	44	
Adjusted for age	1.00 (referent)	0.90 (0.65 to 1.30)	0.85 (0.60 to 1.20)	0.89 (0.63 to 1.30)	0.72 (0.50 to 1.10)	.10
Multivariable adjusted†	1.00 (referent)	0.88 (0.63 to 1.20)	0.81 (0.57 to 1.10)	0.88 (0.62 to 1.20)	0.74 (0.50 to 1.10)	.10
Multivariable adjusted‡	1.00 (referent)	0.87 (0.62 to 1.20)	0.79 (0.56 to 1.10)	0.86 (0.61 to 1.20)	0.72 (0.49 to 1.10)	.10

* *P* values were calculated from two-sided χ^2 tests by modeling lycopene intake as a continuous variable using the median intake for each category.

† Hazard ratios adjusted for age (months), height (<66, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥72.0 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, ≥30.0 kg/m^2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and caloric intake (kcal/day, quintiles).

‡ Hazard ratios adjusted for age (months), height (<66, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥70.0 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25–27.4, 27.5–29.9, ≥30.0 kg/m^2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and dietary intakes of calcium (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), α-linolenic acid (g/day, quintiles), coffee (none, <1, 1–3, 4–5, ≥6 cups/day), and total calories (kcal/day, quintiles).

Table 3. Hazard ratios (HR) and 95% confidence intervals (CIs) of total and lethal prostate cancer in relation to different measurements of dietary lycopene intake in the Health Professionals Follow-up Studyy (1994–January, 2010), among men who had at least one negative prostate-specific antigen test

Measures of dietary lycopene intake	Dietary lycopene intake, HR (95% CI)					P_{trend}*
	Q1	Q2	Q3	Q4	Q5	
Total prostate cancer						
Cumulative average, updated†						
No. of cases	779	803	748	747	691	
Multivariable-adjusted‡	1.00 (referent)	0.98 (0.89 to 1.10)	0.91 (0.82 to 1.00)	0.93 (0.84 to 1.00)	0.90 (0.81 to 1.00)	.03
Multivariable-adjusted§	1.00 (referent)	0.98 (0.89 to 1.10)	0.90 (0.82 to 1.00)	0.92 (0.83 to 1.00)	0.88 (0.79 to 0.98)	.02
Simply updated‖						
No. of cases	816	791	757	705	699	
Multivariable-adjusted‡	1.00 (referent)	0.97 (0.88 to 1.10)	0.99 (0.89 to 1.10)	0.95 (0.86 to 1.10)	0.93 (0.84 to 1.00)	.10
Multivariable-adjusted§	1.00 (referent)	0.97 (0.88 to 1.10)	0.98 (0.89 to 1.10)	0.95 (0.85 to 1.00)	0.92 (0.83 to 1.00)	.09
Baseline¶						
No. of cases		773	772	730	663	
Multivariable-adjusted‡	1.00 (referent)	0.94 (0.85 to 1.00)	0.98 (0.88 to 1.10)	0.93 (0.84 to 1.00)	0.87 (0.78 to 0.96)	.009
Multivariable-adjusted§	1.00 (referent)	0.93 (0.85 to 1.00)	0.97 (0.88 to 1.10)	0.92 (0.83 to 1.00)	0.86 (0.77 to 0.95)	.004
Lethal prostate cancer						
Cumulative average, updated§						
No. of cases	82	59	51	63	31	
Multivariable-adjusted‡	1.00 (referent)	0.75 (0.51 to 1.10)	0.65 (0.43 to 0.98)	0.90 (0.61 to 1.30)	0.48 (0.29 to 0.77)	.01
Multivariable-adjusted§	1.00 (referent)	0.74 (0.50 to 1.10)	0.64 (0.43 to 0.96)	0.88 (0.60 to 1.30)	0.47 (0.29 to 0.75)	.009
Simply updated‖						
No. of cases	73	72	49	53	39	
Multivariable-adjusted‡	1.00 (referent)	1.10 (0.73 to 1.60)	0.85 (0.56 to 1.30)	0.95 (0.63 to 1.40)	0.67 (0.42 to 1.10)	.07
Multivariable-adjusted§	1.00 (referent)	1.10 (0.73 to 1.50)	0.84 (0.56 to 1.30)	0.94 (0.62 to 1.40)	0.66 (0.42 to 1.10)	.06
Baseline¶						
No. of cases	83	62	51	58	32	
Multivariable-adjusted‡	1.00 (referent)	0.82 (0.56 to 1.20)	0.74 (0.50 to 1.10)	0.93 (0.63 to 1.40)	0.50 (0.31 to 0.80)	.01
Multivariable-adjusted§	1.00 (referent)	0.81 (0.55 to 1.20)	0.74 (0.49 to 1.10)	0.92 (0.62 to 1.40)	0.48 (0.30 to 0.78)	.009

* *P* values were calculated from two-sided χ^2 tests by modeling lycopene intake as a continuous variable using the median intake for each category.

† Cumulative average of lycopene intake from 1986 to 2006 or to the questionnaire year before cancer diagnosis.

‡ Hazard ratios adjusted for age (months), height (<66.0, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥70 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, ≥30.0 kg/m2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and caloric intake (kcal/day, quintiles).

§ Hazard ratios adjusted for age (months), height (<66.0, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥72.0 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, ≥30 kg/m2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and dietary intakes of calcium (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), α-linolenic acid (g/day, quintiles), coffee (none, <1, 1–3, 4–5, ≥6 cups/day), and total calories (kcal/day, quintiles).

‖ The most recent lycopene intake before cancer diagnosis.

¶ Lycopene intake in 1986.

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) of prostate cancer in relation to different measurements of dietary lycopene intake in the Health Professionals Follow-up Study (1994–January, 2010) among men who had at least one negative prostate-specific antigen test

	Dietary lycopene intake, HR (95% CI)					
Models	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}*
Total prostate cancer						
Model 1†						
Cumulative average, updated‡	1.00 (referent)	0.97 (0.87 to 1.10)	0.89 (0.79 to 1.00)	0.92 (0.80 to 1.00)	0.89 (0.76 to 1.00)	.10
Simply updated§	1.00 (referent)	1.00 (0.90 to 1.10)	1.00 (0.93 to 1.20)	1.00 (0.90 to 1.20)	1.00 (0.87 to 1.20)	1.00
Model 2‖						
Cumulative average, updated‡	1.00 (referent)	0.97 (0.87 to 1.10)	0.89 (0.78 to 1.00)	0.90 (0.79 to 1.00)	0.87 (0.75 to 1.00)	.08
Simply updated§	1.00 (referent)	0.99 (0.90 to 1.10)	1.00 (0.93 to 1.20)	1.00 (0.90 to 1.20)	1.00 (0.88 to 1.20)	.90
Model 3†						
Baseline¶	1.00 (referent)	0.94 (0.85 to 1.00)	0.98 (0.88 to 1.10)	0.94 (0.84 to 1.00)	0.88 (0.78 to 0.98)	.03
Simply updated§	1.00 (referent)	0.99 (0.89 to 1.10)	1.00 (0.90 to 1.10)	0.98 (0.88 to 1.10)	0.97 (0.87 to 1.10)	.60
Model 4‖						
Baseline¶	1.00 (referent)	0.94 (0.85 to 1.00)	0.97 (0.88 to 1.10)	0.93 (0.83 to 1.00)	0.87 (0.78 to 0.97)	.02
Simply updated§	1.00 (referent)	0.99 (0.89 to 1.10)	1.00 (0.90 to 1.10)	0.98 (0.88 to 1.10)	0.97 (0.86 to 1.10)	.50
Model 5†						
Cumulative average, updated‡	1.00 (referent)	1.00 (0.89 to 1.10)	0.92 (0.82 to 1.00)	0.97 (0.85 to 1.10)	0.96 (0.83 to 1.10)	.70
Baseline¶	1.00 (referent)	0.95 (0.85 to 1.10)	1.00 (0.90 to 1.10)	0.96 (0.85 to 1.10)	0.89 (0.78 to 1.00)	.10
Model 6‖						
Cumulative average, updated‡	1.00 (referent)	0.99 (0.89 to 1.10)	0.92 (0.81 to 1.00)	0.96 (0.84 to 1.10)	0.95 (0.82 to 1.10)	.50
Baseline¶	1.00 (referent)	0.95 (0.85 to 1.10)	1.00 (0.89 to 1.10)	0.96 (0.84 to 1.10)	0.89 (0.77 to 1.00)	.10
Lethal prostate cancer						
Model 1†						
Cumulative average, updated‡	1.00 (referent)	0.66 (0.42 to 1.00)	0.58 (0.35 to 0.97)	0.80 (0.46 to 1.40)	0.45 (0.22 to 0.90)	.07
Simply updated§	1.00 (referent)	1.30 (0.86 to 2.00)	1.20 (0.70 to 2.00)	1.30 (0.71 to 2.20)	1.10 (0.56 to 2.20)	.80
Model 2‖						
Cumulative average, updated‡	1.00 (referent)	0.65 (0.42 to 1.00)	0.57 (0.34 to 0.95)	0.79 (0.45 to 1.40)	0.44 (0.22 to 0.88)	.06
Simply updated§	1.00 (referent)	1.30 (0.86 to 2.00)	1.20 (0.71 to 2.00)	1.30 (0.71 to 2.20)	1.10 (0.56 to 2.20)	.80
Model 3†						
Baseline¶	1.00 (referent)	0.80 (0.54 to 1.20)	0.76 (0.49 to 1.20)	0.94 (0.62 to 1.40)	0.53 (0.32 to 0.90)	.05
Simply updated§	1.00 (referent)	1.20 (0.78 to 1.70)	0.96 (0.62 to 1.50)	1.10 (0.67 to 1.70)	0.85 (0.51 to 1.40)	.50
Model 4‖						
Baseline¶	1.00 (referent)	0.79 (0.53 to 1.20)	0.75 (0.49 to 1.20)	0.93 (0.61 to 1.40)	0.52 (0.31 to 0.88)	.04
Simply updated§	1.00 (referent)	1.20 (0.78 to 1.70)	0.95 (0.61 to 1.50)	1.00 (0.67 to 1.60)	0.85 (0.51 to 1.40)	.40
Model 5†						
Cumulative average, updated‡	1.00 (referent)	0.77 (0.50 to 1.20)	0.68 (0.41 to 1.10)	0.94 (0.55 to 1.60)	0.62 (0.31 to 1.20)	.40
Baseline¶	1.00 (referent)	0.94 (0.61 to 1.20)	0.91 (0.55 to 1.50)	1.10 (0.63 to 1.80)	0.66 (0.34 to 1.30)	.30
Model 6‖						
Cumulative average, updated‡	1.00 (referent)	0.77 (0.49 to 1.20)	0.67 (0.40 to 1.10)	0.93 (0.55 to 1.60)	0.61 (0.31 to 1.20)	.30
Baseline¶	1.00 (referent)	0.92 (0.60 to 1.40)	0.90 (0.55 to 1.50)	1.10 (0.62 to 1.80)	0.65 (0.33 to 1.30)	.30

* *P* values were calculated from two-sided χ^2 tests by modeling lycopene intake as a continuous variable using the median intake for each category.

† Hazard ratios adjusted for age (months), height (<66.0, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥70 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, ≥30.0kg/m^2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and caloric intake (kcal/day, quintiles).

‡ Cumulative average of lycopene intake from 1986 to 2006 or to the questionnaire year before cancer diagnosis.

§ The most recent lycopene intake before cancer diagnosis.

‖ Hazard ratios adjusted for age (months), height (<66.0, 66.0–67.9, 68.0–69.9, 70.0–71.9, ≥72.0 inches), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, ≥30 kg/m2), race (black, white, Asian, other), family history of prostate cancer (yes or no), vigorous activity (none, 0–3.4, 3.5–10.4, 10.5–28.4, ≥28.5 MET hours/week), smoking status (never; past and quit >10 years; past and quit ≤10 years; current; missing), and dietary intakes of calcium (500–749, 750–999, 1000–1499, 1500–1999, ≥2000 mg/day), α-linolenic acid (g/day, quintiles), coffee (none, <1, 1–3, 4–5, ≥6 cups/day), and total calories (kcal/day, quintiles).

¶ Lycopene intake in 1986.

models with or without dietary intakes of calcium, alpha-linolenic acid, and coffee yielded similar results. The associations persisted for baseline intake and cumulative average of intake and did not persist for simply updated intake. These results support that measures of long-term or early dietary lycopene intake are more relevant for prevention against prostate cancer, especially aggressive cancers.

Table 5 presents the association between quintiles of lycopene intake and levels of tumor markers for angiogenesis, apoptosis, and cellular proliferation and differentiation. There was no association between intake and extent of tumor apoptosis and cellular proliferation or differentiation. However, three of the tumor angiogenesis markers, microvessel diameter and area and irregularity of the vessel lumen, as well as the summary angiogenic score, were strongly associated with lycopene intake in such a way that men with higher lycopene intake had tumors that displayed less angiogenic potential. Because lycopene intake and angiogenesis are both associated with tumor stage, we evaluated the relation between angiogenic measures and lycopene intake in tumors confined within the prostate or with limited extraprostatic extension (T1–T3a, N0, M0) to minimize the effect of tumor stage. Statistically significant trends persisted for all three angiogenic markers and the score.

Discussion

In this study, lycopene intake was inversely associated with incidence of total prostate cancer and lethal prostate cancer. In addition, we evaluated tumor biomarkers for various cellular and molecular events in relation to lycopene intake and found that higher lycopene intake was associated with lower angiogenic potential in the tumor based on the vessel size and shape. Based on these results, we hypothesize that the consumption of a diet rich in lycopene-containing foods reduces the aggressive potential of prostate cancer by inhibiting the neoangiogenesis that occurs in tumor development.

Several factors may have contributed to the fact that we observed the strongest association for lycopene intake in the analysis restricted to those with a negative PSA test at baseline. In this analytic design, subsequent diagnosis of prostate cancer, typically resulting from a rise in PSA, may represent a true change in the activity of the cancer. In studies where there are many prevalent cases, as in the initial use of PSA screening, the cancer may have been prevalent for many years and the exposure over the study period would not be expected to influence the cancer. Further, the potential for detection bias is diminished in this analysis.

Because of mixed evidence in the literature, the role of tomato products and lycopene in prostate cancer etiology and prevention remained controversial. In 2007, the US Food and Drug Administration published an evidence-based review of tomato, lycopene, and cancer and concluded that there is "very limited evidence to support an association between tomato consumption and reduced risk of prostate cancer" (39). In contrast, several months later, the World Cancer Research Fund suggested that their systematic review of the literature supported a likely relationship (40). Findings in our study and others support an inverse association between lycopene-rich foods and prostate cancer, particularly for lethal disease. Several factors may contribute to this inconsistency.

First, measurement for bioavailable lycopene may be imprecise in many studies (41). The bioavailability of lycopene varies greatly in food sources. When tomato and certain fruits are consumed raw, the absorption of lycopene may be lower. Food processing and cooking greatly enhances the bioavailability of lycopene by

Table 5. Tumor markers (angiogenesis, apoptosis, proliferation, and differentiation) by quintiles of dietary lycopene intake in the Health Professionals Follow-up Study cohort

		Dietary Lycopene intake (cumulative average, updated)					
Tumor biomarkers	**Overall**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}*
All tumors							
Angiogenesis–CD34 staining	570	136	116	118	114	86	
Vessel diameter†, μm, mean (SD)	12.0 (2.5)	11.2 (2.2)	12.1 (2.4)	12.2 (2.6)	12.3 (3.0)	12.3 (2.0)	.0007
Vessel area†, μm^2, mean (SD)	121.4 (62.4)	101.7 (48.3)	124.5 (61.9)	125.0 (59.7)	133.0 (81.3)	128.4 (50.7)	.0001
Irregularity of vessel lumen‡, mean (SD)	4.03 (1.1)	4.3 (1.0)	4.2 (1.1)	3.8 (1.0)	3.9 (1.1)	3.9 (1.2)	.0002
Angiogenic score§, mean (SD)	0 (0.95)	−0.32 (0.78)	0.04 (0.91)	0.07 (0.94)	0.16 (1.21)	0.12 (0.77)	.0007
Apoptosis–TUNEL assay	454	106	98	97	93	60	
Percentage of stained area, mean (SD)	2.2 (4.7)	2.6 (5.3)	1.9 (3.9)	2.0 (4.1)	1.5 (3.4)	3.2 (1.0)	.70
Cell proliferation–Ki-67 staining	372	85	70	83	79	55	
Number of positive nuclei, mean (SD)	10.5 (32.4)	7.9 (11.7)	13.1 (40.1)	10.3 (23.4)	7.1 (8.2)	16.6 (62.7)	.80
Percentage of positive nuclei, mean (SD)	0.75 (1.7)	0.61 (0.98)	0.73 (1.4)	0.89 (2.0)	0.58 (0.89)	1.0 (2.8)	.90
Cell differentiation–tumor grade	1007	207	202	216	209	173	
Gleason score, mean (SD)	7.2 (0.93)	7.2 (0.91)	7.2 (0.95)	7.3 (0.97)	7.2 (0.93)	7.1 (0.88)	.60
Organ-confined tumors							
Angiogenesis–CD34 staining	360	82	73	75	71	59	
Vessel diameter†, μm, mean (SD)	12.2 (2.5)	11.3 (2.0)	12.2 (2.3)	12.5 (2.8)	12.9 (3.0)	12.1 (1.8)	.01
Vessel area†, μm^2, mean (SD)	125.7 (64.6)	102.1 (42.6)	126.1 (65.5)	132.7 (63.7)	147.4 (87.5)	122.8 (46.1)	.002
Irregularity of vessel lumen‡, mean (SD)	4.0 (1.1)	4.3 (1.0)	4.2 (1.1)	3.7 (1.0)	3.7 (1.1)	3.8 (1.1)	.0001
Angiogenic score§, mean (SD)	0.07 (0.96)	−0.29 (0.70)	0.07 (0.93)	0.19 (1.0)	0.39 (1.3)	0.03 (0.7)	.007

* P_{trend} was calculated using analysis of variance and was two-sided.

† Smaller vessels are more angiogenic.

‡ Irregular vessels are more angiogenic; a score of 1.0 indicates a perfect circle.

§ Lower angiogenic scores are more angiogenic.

disrupting its binding to matrices and making the highly lipophilic lycopene readily available for intestinal absorption (42,43). Our dietary assessments of lycopene intake, capturing a fourfold increase in the mean values across quintiles, corresponded to a substantial difference (37%) in plasma lycopene concentrations.

Second, the dietary intake of lycopene was repeatedly measured in our cohort, compared with a single assessment in the majority of other studies. With the use of cumulative average of lycopene intake, we were able to capture the changes in diet over time and to reduce within-person variation. We also compared different measures of dietary lycopene intake, including baseline and simply updated lycopene intake, in addition to the cumulative average. Lycopene intake at baseline yielded an inverse association with prostate cancer similar to that with the cumulative average, suggesting that long-term or remote lycopene intake was more etiologically relevant than recent intake.

Third, the distributions of lycopene intake vary greatly across populations. In our study, the median values of energy-adjusted lycopene intake for quintiles were 3160, 5101, 6744, 8923, and 13 391 μg/day, with a fourfold difference in the median values between the highest and lowest quintiles. In a hospital-based case–control study in Uruguay (14), the investigators evaluated various foods and nutrients in relation to risk of prostate cancer and observed no association with lycopene. However, the ranges of lycopene intake quartiles were 1300 or less, 1301 to 2501, 2502 to 3300, and more than 3301 μg/day. Dietary intake of lycopene in this population may have been too low to be informative.

Fourth, the association between lycopene intake and prostate cancer risk was weak for endpoints enriched with indolent cancers (eg, total prostate cancer in the PSA era), stronger for lethal prostate cancer than for total prostate cancer, and particularly strong when restricted to men who have had at least one negative PSA test at baseline. This overall pattern suggests that lycopene may be primarily influencing progression of prostate cancers. Similar to our results, studies conducted in the United States before the widespread use of PSA screening (4) or in other areas where the PSA screening is not prevalent (18,24) generally support a positive role of lycopene in prostate cancer prevention. In settings where incident cases were primarily diagnosed through PSA screening, the studies generally yielded null findings (7,12). Further, in the observational study component of the Prostate Cancer Prevention Trial (8,19), a reanalysis showed no association between lycopene level and cancers that had shown no evidence of progression but were detected by an end-of-study biopsy, but lycopene was associated with cancers that showed signs of progression during the study through symptoms, growth, or rise in PSA (44).

Interestingly, corresponding to the suggestion that lycopene influences primarily progression of prostate cancer, we found that dietary lycopene intake was correlated with less angiogenic potential in the tumor. Previously in the HPFS, we reported that microvessel morphological markers, such as microvessel diameter and area, and the irregularity of the vessel lumen, strongly predict lethal prostate cancer (34). Of note, angiogenic factors correlated with stage and lethality largely independently of grade, suggesting that factors that influence progression through angiogenesis would do so largely independently of tumor grade.

To our knowledge, this is the first epidemiological study to report the potential antiangiogenic effect of lycopene-rich foods. Lycopene may inhibit angiogenesis of prostate cancer cells by regulating vascular endothelial growth factor (45). Elgass et al., using human umbilical vein endothelial cells, reported that lycopene inhibited in vitro angiogenesis at physiologically relevant concentrations (46). Huang et al. reported that the antiangiogenic effects of lycopene were mediated through immunomodulation of proangiogenic cytokine secretion in human peripheral blood mononuclear cells (47). Chen et al. showed the antiangiogenic activity of lycopene both in vitro and in vivo and proposed that the mechanism may involve PI3K-Akt and ERK/p38 signaling pathways (48).

As for all observational studies, the main limitation is the potential for uncontrolled confounding by unknown factors. Although this possibility could not be ruled out entirely, the likelihood that uncontrolled confounders entirely accounted for our results on lycopene and prostate cancer is low. Humans consume lycopene through specific food sources, such as tomato and tomato-based products, which is only a small component of the entire diet. These foods are not strongly associated with other lifestyle or dietary factors (see Table 1). Age-adjusted analyses, multivariable analyses adjusting for lifestyle factors, and multivariable analyses adjusting for both lifestyle and dietary factors yielded very similar results. Measurement error is also a factor in nutritional studies, but as discussed above, several features of our study design, including repeated measures, may have minimized error. Finally, our cohort is comprised of mainly white health professionals, which may limit generalizability of our results.

In conclusion, our results suggest the intake of lycopene is associated with reduced risk of lethal prostate cancer. In the setting of widespread PSA screening, advanced or lethal prostate cancer is preferable to total prostate cancer as the endpoint for epidemiological studies of lycopene.

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