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Original Contribution

Diet, Supplement Use, and Prostate Cancer Risk: Results From the Prostate Cancer Prevention Trial

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The authors examined nutritional risk factors for prostate cancer among 9,559 participants in the Prostate Cancer Prevention Trial (United States and Canada, 1994–2003). The presence or absence of cancer was determined by prostate biopsy, which was recommended during the trial because of an elevated prostate-specific antigen level or an abnormal digital rectal examination and was offered to all men at the trial's end. Nutrient intake was assessed using a food frequency questionnaire and a structured supplement-use questionnaire. Cancer was detected in 1,703 men; 127 cancers were high-grade (Gleason score 8–10). There were no associations of any nutrient or supplement with prostate cancer risk overall. Risk of high-grade cancer was associated with high intake of polyunsaturated fats (quartile 4 vs. quartile 1: odds ratio = 2.41, 95% confidence interval (CI): 1.33, 4.38). Dietary calcium was positively associated with low-grade cancer but inversely associated with high-grade cancer (for quartile 4 vs. quartile 1, odds ratios were 1.27 (95% CI: 1.02, 1.57) and 0.43 (95% CI: 0.21, 0.89), respectively). Neither dietary nor supplemental intakes of nutrients often suggested for prostate cancer prevention, including lycopene, long-chain n-3 fatty acids, vitamin D, vitamin E, and selenium, were significantly associated with cancer risk. High intake of n-6 fatty acids, through their effects on inflammation and oxidative stress, may increase prostate cancer risk.

diet; dietary supplements; food; micronutrients; prostatic neoplasms

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; DRE, digital rectal examination; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; PCPT, Prostate Cancer Prevention Trial; PSA, prostate-specific antigen.

Sound biologic reasoning underlies the hypothesis that dietary patterns, through their effects on steroid hormone and xenobiotic metabolism, oxidative stress, and inflammation, can modify prostate cancer risk. However, the findings from observational and experimental studies examining diet and prostate cancer risk are inconsistent. For example, several cohort studies and secondary analyses from randomized clinical trials found inverse associations of selenium and vitamin E supplementation with prostate cancer risk (1, 2), often restricted to subsets of men such as smokers (3) or men with specific genotypes (4), but a large randomized clinical trial did not find reduced risks after supplementation with vitamin E, selenium, or both (5). Inverse associations found for dietary lycopene in some cohorts (6, 7) have not been consistently corroborated in studies using serum lycopene as a biomarker of intake (8, 9). Both dietary and supplemental calcium have been associated with increased risk in many observational studies (10, 11), but calcium supplementation was found to be protective in a randomized clinical trial (12).

Many factors could explain the discrepancies across these studies. Most important is the widespread adoption of prostate-specific antigen (PSA) screening, which has caused the preponderance of incident prostate cancer cases to be asymptomatic, local-stage, and of uncertain clinical importance (13). It is thus critical to accurately assess the phenotypes of local-stage disease, which currently is best characterized by Gleason grade (14). A related concern is detection bias. The strongest predictor of being diagnosed with prostate cancer is the receipt of PSA screening (15), yet substantial numbers of men with PSA levels below the standard 4.0-ng/mL cutpoint for diagnostic evaluation have prostate cancer that is undiagnosed (16). Thus, if investigators do not carefully control for screening in their analyses, factors associated with the use of screening or serum PSA level could obscure or confound etiologic associations.

Here we present results from a study examining the associations of nutrient intake from food and supplements with the 7-year period prevalence of prostate cancer in a large cohort of men participating in the Prostate Cancer Prevention Trial (PCPT). Several aspects of the PCPT are unique, particularly the biopsy-determined absence or presence of cancer and the centralized and uniform pathologic grading used to define cancer endpoints. Thus, while almost all prostate cancer cases were local-stage, detection bias was minimized and pathologic grading of cases was rigorous and standardized. Analytical results given here are focused on the nutrients and phytochemicals that have been associated with prostate cancer risk in previous studies, including macronutrient density, lycopene, calcium, folate, vitamin D, and n-3 fatty acids.

MATERIALS AND METHODS

Study design and study population

The PCPT (http://www.cancer.gov/pcpt) was a randomized, placebo-controlled trial that tested whether finasteride, a 5α-reductase inhibitor, could reduce the 7-year period prevalence of prostate cancer (16). Briefly, beginning in 1993, 18,880 US and Canadian men aged 55 years or older with normal digital rectal examination (DRE) results, PSA levels of 3 ng/mL or less, and no history of prostate cancer, severe lower urinary tract symptoms, or clinically significant coexisting conditions were randomized to receive finasteride (5 mg/day) or placebo. During the PCPT, men underwent DRE and PSA determination annually, and a prostate biopsy was recommended for participants with an abnormal DRE or a PSA level (adjusted for the effect of finasteride) of 4.0 ng/mL or greater. At the final study visit in year 7 (2000–2003), all men not previously diagnosed with prostate cancer were offered a biopsy, which consisted of a minimum of 6 core samples collected under transrectal ultrasonographic guidance. Biopsies were reviewed for adenocarcinoma by both the pathologist at the local study site and a central pathology laboratory, with full concordance. Clinical stage was assigned locally, and tumors were graded centrally using the Gleason scoring system (14).

Of the 18,880 participants, we excluded 7,615 (40.3%) who did not have an end-of-study biopsy, including 1,225 men who died, 6,381 who were medically unable to have a biopsy or refused, and 9 who underwent prostatectomy for reasons other than cancer; this left 2,401 cases and 8,864 noncases. We then excluded 173 cases diagnosed on or after the trial end date (June 24, 2003), 92 cases diagnosed 180 days or more after their planned end-of-study visit, and 140 cases who were missing Gleason scores. From the 10,860 men remaining for study, we further excluded 102 men who were missing data on body mass index, 770 men who were missing dietary data, and 429 men whose dietary information was judged to be unreliable because of a reported energy intake less than 800 kcal/day or greater than 5,000 kcal/day. Some men did not complete dietary questionnaires because practitioners at their clinical site chose not to participate in the dietary studies or because prostate cancer was diagnosed before the questionnaire was administered. This analysis was based on 1,703 cancer cases diagnosed in 9,559 men.

Data collection

Details regarding demographic and health-related characteristics were collected at baseline using self-administered questionnaires. Level of physical activity was assessed using a 6-item questionnaire (17). Height and weight were measured at the baseline clinic visit.

One year after randomization, the men filled in a 15-page booklet containing 2 questionnaires on diet and the use of nutritional supplements. Diet was assessed using a food frequency questionnaire (FFQ) developed specifically for this population of older men. The FFQ consisted of questions on 99 foods and 9 beverages, plus 18 questions on food preparation and 2 questions on consumption of fruits and vegetables. Algorithms for analysis of data from this questionnaire are available at http://www.fhcrc.org/science/shared_resources/nutrition/ffq/tech_doc.pdf. The nutritional supplement questionnaire has been described in detail previously (18). On the questionnaire, participants reported: the usual number of pills taken per day for multivitamins and antioxidant mixtures; both the number of pills taken per day and the dose for β-carotene, vitamin C, vitamin E, calcium, and zinc; and whether they used stress-type multivitamins, vitamin D, fish oil, or selenium at least 3 times per week. Multivitamin use and supplemental intakes of specific nutrients (the sum of single supplements plus multivitamins) were categorized as low (corresponding to no use or infrequent use of a supplement), moderate (corresponding to the amounts generally obtained from multivitamins), and high (corresponding to amounts that are generally only possible from using high-dose single supplements). Because data for fish oil, selenium, and vitamin D were available only on whether these supplements were used at least 3 times per week, fish oil was coded as 0 or 0.5 g of docosahexaenoic (DHA) plus eicosapentaenoic (EPA) fatty acids per day, selenium was coded as 0 or 200 μg/day, and vitamin D was coded as 0 or 10 μg/day. The vitamin D content of multivitamins is also 10 μg; thus, men who used both multivitamins and single vitamins were placed in the high-dose vitamin D category.

In an inter- and intramethod reliability study carried out among 150 randomly selected men, we compared nutrient intakes calculated from the initial FFQ, intakes from 6 24-hour recalls administered over the following year, and intakes from an additional FFQ completed after all 24-hour recalls had been administered. Based on the 128 men who completed the study, correlations between the first FFQ and the 24-hour recalls (adjusted for energy and deattenuated for measurement error (19)) were: total fat, 0.71; polyunsaturated fat, 0.66; monounsaturated fat, 0.66; saturated fat, 0.75; alcohol, 0.84; carbohydrate, 0.70; protein, 0.50; vitamin C, 0.62; lycopene, 0.58; β-carotene, 0.68; vitamin D, 0.57; EPA + DHA, 0.87; calcium, 0.62; and zinc, 0.51. Correlations between repeat FFQs were above 0.60 for all nutrients, with the exception of 0.54 for EPA + DHA.

Statistical analysis

We used logistic and polytomous logistic regression models to estimate associations of diet and supplement use with risks of total, low-grade (Gleason score 2–7), and high-grade (Gleason score 8–10) prostate cancer. Several alternative categorizations of grade (Gleason score 2–6 vs. 7–10; Gleason score 2–6 vs. 7 vs. 8–10; and Gleason score 2–6 (3 + 4) vs. (4 + 3) 8–10) were examined, but findings were limited to Gleason score 8–10, with no difference between Gleason scores categorized as 2–6 and 2–7. Results given were adjusted for age (continuous), race/ethnicity (white, African-American, other), family history of prostate cancer in first-degree relatives (yes, no), treatment arm (finasteride, placebo), and body mass index (weight (kg)/height $(m)^2$; continuous). Further control for education, diabetes, current smoking, and physical activity did not affect the results, and these factors were not included in the final models. Tests for linear trend across categories were based on an ordinal variable, as described by Breslow and Day (20). Results are given for both study arms combined, because in preliminary analyses there were no discordant findings between arms. All analyses used SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Table 1 shows the demographic and health-related characteristics of the study population. Older age, African-American race/ethnicity, and family history of prostate cancer were associated with increased prostate cancer risk; high body mass index was associated with lower risk of total cancer, but in previously published results, the associations were inverse for low-grade disease and positive for high-grade disease (21). The majority of prostate cancers were low-grade and in an early clinical stage.

There were no significant associations of any nutrient or nutritional supplement with the risk of total prostate cancer; therefore, results are given by grade only. Table 2 shows adjusted odds ratios for low- and high-grade prostate cancer associated with energy and micronutrient intake.

For each macronutrient, we present results from 2 statistical models, labeled ''Percent energy'' and ''Total energy.'' In the percent energy models, we examined the percentage of energy derived from each macronutrient (for alcohol, models used categorized numbers of drinks per week) and used a linear term for total energy as a covariate; results from this model are interpreted as the effect of substituting energy from each specific macronutrient for other macronutrients. The total energy models examined energy from each macronutrient, and those results can be interpreted as the effect of increasing energy from a specific macronutrient while keeping the energy from other macronutrients constant. In both the percent energy models and the total energy models, there were no associations of energy, carbohydrate, or protein with risk of either high- or low-grade cancer. In the percent energy models, men in the highest category of alcohol intake (≥14 drinks/week) had a 73% increased risk of high-grade cancer in comparison with nondrinkers ($P < 0.04$); in total energy models, this increase was 63% ($P < 0.06$). Intake of polyunsaturated fat was positively and significantly associated with risk of high-grade disease: In the percent energy models, there were significant risk increases of approximately 140% in quartiles 2–4 as compared with quartile 1 (all P's < 0.005), with no dose-response; in the total energy model, there was a significant dose-response, with a nearly 190% increased risk of high-grade disease in quartile 4 as compared with quartile 1 ($P < 0.015$).

We completed additional analyses to better characterize the findings specific to polyunsaturated fat and high-grade cancer. In a model examining the effect of substituting polyunsaturated fats for saturated fats, substitution of each percentage point of energy from polyunsaturated fat for saturated fat was associated with a 23% (95% confidence interval (CI): 9, 39) increased risk of high-grade disease. In a model examining the effects of adding energy from each type of fat while keeping energy from all other macronutrients and other types of fat constant, only the coefficient for polyunsaturated fat and high-grade disease was statistically significant ($P < 0.005$), yielding an estimate of a 132% (95% CI: 30, 314) increased risk of high-grade disease associated with each 100-kcal/day increase in energy from polyunsaturated fat.

Table 3 shows the associations of dietary supplement use with cancer risk. There were no significant associations of multivitamin or single supplement use with risk of either low- or high-grade prostate cancer.

Table 4 shows associations for selected micronutrients and food components hypothesized to be associated with prostate cancer risk. Results are given for dietary intake alone and total intake (diet plus supplements) where appropriate. Results for dietary vitamin E and selenium are not reported because, based on very poor correlations between FFQ-based dietary intakes of these nutrients and serum concentrations (22–27), we believe they cannot be assessed using an FFQ. There were significant associations of dietary calcium intake with prostate cancer risk which differed between low- and high-grade disease and showed no evidence of dose-response. For low-grade cancer, men in quartile 4 had a 27% higher risk ($P < 0.04$) than those in quartile 1. For high-grade cancer, men in quartiles 2, 3, and 4 all had significantly lower risks than those in quartile 1, and in a post-hoc analysis, the odds ratio comparing quartiles 2–4 with quartile 1 was 0.52 (95% CI: 0.33, 0.82). In analyses of total calcium intake, the association with low-grade disease was attenuated and no longer statistically significant, but the association with high-grade disease

Table 1. Demographic and Health-Related Characteristics of Prostate Cancer Cases and Controls, Prostate Cancer Prevention Trial, 1994–2003

	Cases (*n* = 1,703)			Controls (*n* = 7,856)			*P* Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, years							
Mean			63.6 (5.6)			62.6 (5.4)	<0.001
<60	480	28.2		2,648	33.7		<0.001
60–64	531	31.2		2,544	32.4		
65–69	418	24.5		1,715	21.8		
≥70	274	16.1		949	12.1		
Race/ethnicity							
White	1,587	93.2		7,372	93.8		<0.001
African-American	75	4.4		210	2.7		
Asian/Pacific Islander	5	0.3		52	0.7		
Hispanic	32	1.9		185	2.4		
Other	4	0.2		37	0.5		
Family history of prostate cancer	374	22.0		1,242	15.8		<0.001
Smoking							
Never smoker	612	35.9		2,701	34.4		0.473
Former smoker	979	57.5		4,629	58.9		
Current smoker	112	6.6		526	6.7		
Diabetes mellitus	72	4.2		550	7.0		<0.001
Finasteride study arm	696	40.9		3,961	50.4		<0.001
Body mass index[b]							
Mean			27.4 (4.0)			27.6 (4.0)	0.023
<25	482	28.3		2,014	25.6		<0.001
25–29	868	51.0		4,063	51.7		
30–34	272	16.0		1,392	17.7		
≥35	81	4.8		387	4.9		
Histologic grade							
Low (GS 2–6)	1,225	71.9					
Moderate (GS 3 + 4)	266	15.6					
Moderate (GS 4 + 3)	85	5.0					
High (GS 8–10)	127	7.5					
Clinical stage							
T1a	215	12.6					
T1b	118	6.9					
T1c	901	52.9					
T2a	234	13.7					
T2b	93	5.5					
T2c	73	4.3					
T3	27	1.6					
T4	0						
Unknown	42	2.5					

Abbreviations: GS, Gleason score; SD, standard deviation.
[a] *t* tests for mean values and chi-squared tests for categories.
[b] Weight (kg)/height (m)^2.

was unchanged. No antioxidant micronutrient or phytochemical, including vitamin C, nonlycopene carotenoids, lycopene, or EPA + DHA, was associated with prostate cancer risk. There was modest evidence that high dietary

Table 2. Associations of Daily Energy and Macronutrient Intake With the Risk of Low- and High-Grade Prostate Cancer, Prostate Cancer Prevention Trial, 1994–2003

	Quartile of Energy or Macronutrient Intake[a]				*P* for Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Energy, kcal	<1,558	1,558–2,066	2,067–2,678	>2,678	
OR (95% CI) for GS 2–7	1.00 (referent)	0.97 (0.83, 1.13)	1.00 (0.85, 1.17)	1.07 (0.92, 1.25)	0.341
No. of cases/total	375/2,227	390/2,405	397/2,398	414/2,402	
OR (95% CI) for GS 8–10	1.00 (referent)	0.98 (0.61, 1.58)	1.00 (0.62, 1.62)	0.69 (0.40, 1.17)	0.226
No. of cases/total	35/1,887	35/2,050	34/2,035	23/2,011	
Total fat					
Percent energy	<27.4	27.4–32.7	32.8–37.9	>37.9	
OR (95% CI) for GS 2–7	1.00 (referent)	0.98 (0.84, 1.15)	0.99 (0.85, 1.16)	0.90 (0.77, 1.06)	0.242
No. of cases/total	407/2,390	397/2,345	397/2,324	375/2,373	
OR (95% CI) for GS 8–10	1.00 (referent)	1.81 (1.08, 3.03)	1.51 (0.87, 2.59)	1.36 (0.78, 2.39)	0.490
No. of cases/total	23/2,006	41/1,989	33/1,960	30/2,028	
Total energy, kcal	<454	454–654	655–919	>919	
OR (95% CI) for GS 2–7	1.00 (referent)	1.05 (0.89, 1.23)	0.92 (0.77, 1.09)	1.07 (0.86, 1.33)	0.963
No. of cases/total	386/2,305	402/2,319	371/2,411	417/2,397	
OR (95% CI) for GS 8–10	1.00 (referent)	1.30 (0.78, 2.16)	1.38 (0.78, 2.43)	1.23 (0.58, 2.60)	0.463
No. of cases/total	31/1,950	36/1,953	35/2,075	25/2,005	
Saturated fat					
Percent energy	<8.5	8.5–10.4	10.5–12.4	>12.4	
OR (95% CI) for GS 2–7	1.00 (referent)	0.89 (0.76, 1.04)	0.95 (0.81, 1.10)	0.89 (0.76, 1.05)	0.282
No. of cases/total	414/2,341	380/2,367	402/2,372	380/2,352	
OR (95% CI) for GS 8–10	1.00 (referent)	1.18 (0.74, 1.87)	0.79 (0.47, 1.33)	0.73 (0.43, 1.26)	0.125
No. of cases/total	34/1,961	41/2,028	28/1,998	24/1,996	
Total energy, kcal	<144	144–209	210–301	>301	
OR (95% CI) for GS 2–7	1.00 (referent)	0.99 (0.84, 1.17)	0.98 (0.80, 1.19)	1.01 (0.77, 1.34)	0.959
No. of cases/total	385/2,280	391/2,334	392/2,399	408/2,419	
OR (95% CI) for GS 8–10	1.00 (referent)	0.93 (0.56, 1.55)	0.73 (0.39, 1.37)	0.37 (0.13, 1.00)	0.103
No. of cases/total	35/1,930	37/1,980	33/2,040	22/2,033	
Monounsaturated fat					
Percent energy	<10.2	10.2–12.5	12.6–14.7	>14.7	
OR (95% CI) for GS 2–7	1.00 (referent)	0.95 (0.81, 1.10)	0.98 (0.84, 1.14)	0.90 (0.77, 1.06)	0.287
No. of cases/total	407/2,355	387/2,355	400/2,330	382/2,392	
OR (95% CI) for GS 8–10	1.00 (referent)	1.68 (1.01, 2.78)	1.30 (0.76, 2.22)	1.14 (0.65, 1.98)	0.984
No. of cases/total	25/1,973	42/2,010	32/1,962	28/2,038	
Total energy, kcal	<170	170–249	250–352	>352	
OR (95% CI) for GS 2–7	1.00 (referent)	0.98 (0.82, 1.16)	0.89 (0.72, 1.10)	1.02 (0.73, 1.42)	0.532
No. of cases/total	395/2,307	388/2,297	377/2,432	416/2,396	
OR (95% CI) for GS 8–10	1.00 (referent)	1.80 (1.04, 3.13)	1.22 (0.58, 2.59)	1.33 (0.41, 4.37)	0.656
No. of cases/total	27/1,939	45/1,954	29/2,084	26/2,006	
Polyunsaturated fat					
Percent energy	<5.4	5.4–6.6	6.7–8.0	>8.0	
OR (95% CI) for GS 2–7	1.00 (referent)	1.04 (0.89, 1.21)	1.02 (0.88, 1.19)	0.95 (0.81, 1.11)	0.507
No. of cases/total	396/2,394	409/2,372	394/2,334	377/2,332	

Table continues

zinc intake was associated with reduced risk of high-grade disease; in a post-hoc analysis, there was a borderline statistically significant ($P = 0.05$) 39% (95% CI: 63, 0) reduced risk of high-grade cancer in quartiles 3–4 as compared with quartiles 1–2. However, there was no association when considering total zinc.

Table 2. Continued

	Quartile of Energy or Macronutrient Intake[a]				*P* for Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
OR (95% CI) for GS 8–10	1.00 (referent)	2.41 (1.33, 4.34)	2.34 (1.29, 4.25)	2.41 (1.33, 4.38)	0.002
No. of cases/total	16/2,014	38/2,001	36/1,976	37/1,992	
Total energy, kcal	<93	93–134	135–191	>191	
OR (95% CI) for GS 2–7	1.00 (referent)	0.91 (0.77, 1.07)	0.95 (0.79, 1.15)	0.88 (0.68, 1.15)	0.474
No. of cases/total	394/2,302	378/2,369	405/2,362	399/2,399	
OR (95% CI) for GS 8–10	1.00 (referent)	1.44 (0.85, 2.45)	1.77 (0.94, 3.32)	2.89 (1.24, 6.73)	0.019
No. of cases/total	30/1,938	34/2,025	31/1,988	32/2,032	
Carbohydrate					
Percent energy	<43.1	43.1–48.6	48.7–54.7	>54.7	
OR (95% CI) for GS 2–7	1.00 (referent)	0.95 (0.81, 1.11)	0.93 (0.80, 1.09)	1.04 (0.89, 1.22)	0.684
No. of cases/total	395/2,342	383/2,349	379/2,359	419/2,382	
OR (95% CI) for GS 8–10	1.00 (referent)	0.96 (0.58, 1.58)	1.05 (0.65, 1.72)	0.82 (0.48, 1.38)	0.557
No. of cases/total	31/1,978	32/1,998	36/2,016	28/1,991	
Total energy, kcal	<755	755–1,005	1,006–1,304	>1,304	
OR (95% CI) for GS 2–7	1.00 (referent)	1.00 (0.85, 1.18)	1.04 (0.87, 1.25)	1.02 (0.82, 1.27)	0.766
No. of cases/total	365/2,211	400/2,398	411/2,420	400/2,403	
OR (95% CI) for GS 8–10	1.00 (referent)	0.80 (0.49, 1.30)	0.67 (0.38, 1.19)	0.64 (0.31, 1.31)	0.171
No. of cases/total	41/1,887	34/2,032	27/2,036	25/2,028	
Protein					
Percent energy	<15.0	15.0–16.9	17.0–18.9	>18.9	
OR (95% CI) for GS 2–7	1.00 (referent)	1.00 (0.86, 1.17)	0.96 (0.82, 1.12)	0.93 (0.79, 1.08)	0.280
No. of cases/total	407/2,338	408/2,376	389/2,373	372/2,345	
OR (95% CI) for GS 8–10	1.00 (referent)	0.82 (0.51, 1.34)	0.78 (0.47, 1.28)	0.82 (0.51, 1.34)	0.412
No. of cases/total	37/1,968	30/1,998	28/2,012	32/2,005	
Total energy, kcal	<258	258–349	350–460	>460	
OR (95% CI) for GS 2–7	1.00 (referent)	0.96 (0.81, 1.13)	0.95 (0.78, 1.14)	0.83 (0.64, 1.07)	0.214
No. of cases/total	379/2,250	401/2,382	406/2,382	390/2,418	
OR (95% CI) for GS 8–10	1.00 (referent)	0.97 (0.58, 1.61)	0.98 (0.54, 1.79)	0.63 (0.26, 1.51)	0.474
No. of cases/total	36/1,907	35/2,016	34/2,010	22/2,050	
Alcohol consumption, drinks/week	<1	1–6	7–13	≥14	
OR (95% CI) for GS 2–7[b]	1.00 (referent)	1.02 (0.89, 1.17)	1.11 (0.94, 1.30)	1.10 (0.92, 1.30)	0.170
No. of cases/total	677/4,179	426/2,577	258/1,447	215/1,229	
OR (95% CI) for GS 8–10[b]	1.00 (referent)	1.01 (0.64, 1.58)	1.20 (0.71, 2.03)	1.73 (1.03, 2.89)	0.055
No. of cases/total	54/3,556	31/2,182	20/1,209	22/1,036	
OR (95% CI) for GS 2–7[c]	1.00 (referent)	1.02 (0.90, 1.17)	1.11 (0.95, 1.30)	1.11 (0.93, 1.31)	0.137
No. of cases/total	677/4,179	426/2,577	258/1,447	215/1,229	
OR (95% CI) for GS 8–10[c]	1.00 (referent)	1.00 (0.64, 1.16)	1.18 (0.70, 2.00)	1.63 (0.98, 2.71)	0.080
No. of cases/total	54/3,556	31/2,182	20/1,209	22/1,036	

Abbreviations: CI, confidence interval; GS, Gleason score; OR, odds ratio.
[a] Results were controlled for age, race/ethnicity, treatment arm, and body mass index.
[b] Results were additionally controlled for total energy intake (substitution of nonalcohol energy for alcohol).
[c] Results were additionally controlled for nonalcohol energy intake (adding energy from alcohol).

DISCUSSION

In this unique study of primarily local-stage prostate cancer, in which the presence or absence of prostate cancer was determined by prostate biopsy, there were no statistically significant associations of nutrient intake or dietary supplement use with prostate cancer overall. When results were stratified by disease grade (low- vs. high-grade disease (Gleason score 2–7 vs. 8–10)), there were several noteworthy associations. Polyunsaturated fat intake was positively

Table 3. Associations of Daily Dietary Supplement Intake With the Risks of Low- and High-Grade Prostate Cancer, Prostate Cancer Prevention Trial, 1994–2003

	Category of Dietary Supplement Intake			*P* for Trend
	Lowest	Moderate	Highest	
Multivitamins, pills/week	<1	1–6	>6	
OR (95% CI) for GS 2–7	1.00 (referent)	1.07 (0.86, 1.33)	1.09 (0.97, 1.22)	0.138
No. of cases/total	858/5,296	112/654	606/3,482	
OR (95% CI) for GS 8–10	1.00 (referent)	0.96 (0.46, 2.01)	1.00 (0.69, 1.45)	0.989
No. of cases/total	73/4,511	8/550	46/2,922	
Vitamin C, mg	<60	60–250	>250	
OR (95% CI) for GS 2–7	1.00 (referent)	1.09 (0.95, 1.26)	1.06 (0.94, 1.21)	0.298
No. of cases/total	688/4,262	381/2,179	507/2,991	
OR (95% CI) for GS 8–10	1.00 (referent)	1.05 (0.66, 1.65)	1.09 (0.72, 1.64)	0.679
No. of cases/total	57/3,631	29/1,827	41/2,525	
Vitamin E, mg	<8	8–30	>30	
OR (95% CI) for GS 2–7	1.00 (referent)	1.05 (0.91, 1.21)	1.08 (0.96, 1.23)	0.199
No. of cases/total	718/4,423	336/1,996	522/3,013	
OR (95% CI) for GS 8–10	1.00 (referent)	0.82 (0.49, 1.35)	1.21 (0.82, 1.78)	0.390
No. of cases/total	59/3,764	21/1,681	47/2,538	
Calcium, mg	<150	150–199	>199	
OR (95% CI) for GS 2–7	1.00 (referent)	1.08 (0.95, 1.23)	1.11 (0.96, 1.29)	0.117
No. of cases/total	917/5,668	381/2,197	278/1,567	
OR (95% CI) for GS 8–10	1.00 (referent)	1.02 (0.66, 1.56)	0.77 (0.46, 1.32)	0.428
No. of cases/total	80/4,831	30/1,846	17/1,306	
Zinc, μg	<15	15–22	>22	
OR (95% CI) for GS 2–7	1.00 (referent)	1.10 (0.97, 1.24)	0.95 (0.79, 1.15)	0.723
No. of cases/total	894/5,467	526/2,974	156/991	
OR (95% CI) for GS 8–10	1.00 (referent)	0.99 (0.67, 1.47)	1.08 (0.62, 1.90)	0.847
No. of cases/total	74/4,647	38/2,486	15/850	
Fish oil, mg	0	0.5		
OR (95% CI) for GS 2–7	1.00 (referent)	1.15 (0.93, 1.42)		0.184
No. of cases/total	1,459/8,805	117/627		
OR (95% CI) for GS 8–10	1.00 (referent)	1.31 (0.70, 2.45)		0.399
No. of cases/total	116/7,462	11/521		
Selenium, μg	<10	10–30	>30	
OR (95% CI) for GS 2–7	1.00 (referent)	1.08 (0.96, 1.22)	1.06 (0.89, 1.25)	0.184
No. of cases/total	870/5,351	514/2,947	192/1,134	
OR (95% CI) for GS 8–10	1.00 (referent)	0.80 (0.53, 1.21)	1.00 (0.58, 1.73)	0.315
No. of cases/total	78/4,559	33/2,466	16/958	
Vitamin D, μg	<2.5	2.5–10	>10	
OR (95% CI) for GS 2–7	1.00 (referent)	1.06 (0.94, 1.19)	1.10 (0.88, 1.38)	0.250
No. of cases/total	874/5,362	601/3,494	101/576	
OR (95% CI) for GS 8–10	1.00 (referent)	0.94 (0.64, 1.37)	1.01 (0.48, 2.10)	0.832
No. of cases/total	75/4,563	44/2,937	8/483	

Abbreviations: CI, confidence interval; GS, Gleason score; OR, odds ratio.

associated with risk of high-grade cancer, and dietary calcium intake was positively associated with risk of low-grade cancer and inversely associated with risk of high-grade cancer. Based on a post-hoc analysis, there was evidence that dietary zinc intake beyond a relatively low threshold was associated with reduced risk of high-grade cancer. There was also some evidence that a high alcohol intake was associated with increased risk of high-grade disease; the associations of alcohol intake with cancer risk in the PCPT are complex and have been described previously (28). Neither use of dietary supplements nor intake of antioxidants, folate, vitamin D, or long-chain n-3 fatty acids was significantly associated with low- or high-grade prostate cancer risk.

Investigators in many large case-control and cohort studies have reported that calcium intake from foods and/or supplements was associated with increased cancer risk (29–34). Our finding of no association with total prostate cancer risk (odds ratios contrasting quartile 4 with quartile 1 were 1.16 (95% CI: 0.95, 1.43) and 1.09 (95% CI: 0.91, 1.32) for dietary intake and total intake, respectively) was consistent with the null findings from several other large cohort studies (35–38). Our finding that calcium intake was inversely associated with high-grade cancer but positively associated with low-grade cancer is inconsistent with several other studies that found associations to be stronger or exclusive for high-grade or advanced-stage disease (29, 31, 32); in particular, we found no evidence that very high dietary calcium intakes (>1,400 mg/day) were associated with increased risk of high-grade disease. Our findings are similar to those reported from the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (33). In both the PCPT and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, and in contrast to other studies, almost all prostate cancers were local-stage and screen-detected. It is possible that risk factors for screen-detected cancers are different from those diagnosed clinically. For example, if we assume that low-grade cancers develop into high-grade cancers, perhaps calcium decreases the rate at which low-grade cancers progress. However, lacking a strong biologic rationale, the calcium findings from both the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the PCPT should be considered provisional until they are replicated in studies that separate screen-detected cancers from clinically detected cancers.

Many investigators have studied associations of dietary fat with prostate cancer risk, and their findings are inconsistent. In a 2004 meta-analysis, Dennis et al. (39) found a significantly increased risk associated with high fat consumption in case-control studies but no association in cohort studies; and in more recently published cohort studies, investigators have found either no associations (40–42) or significant inverse associations for high-grade disease (43). Study results differ somewhat when risk is examined separately by stage and/or grade and when fats are separated into polyunsaturated, monounsaturated, and saturated fats, but overall there is little support for associations of fat with risk. We know of no studies which have found that a high intake of polyunsaturated fat—more specifically, the substitution of polyunsaturated fat for saturated fat—was associated with increased risk of high-grade cancer; however, this finding is biologically plausible. The n-6 fatty acids, which constitute the majority of dietary polyunsaturated fats, are proinflammatory (44), and inflammation may play an important role in prostate cancer pathogenesis (45). A single study of heavy smokers and/or asbestos-exposed men found a substantially increased risk associated with high polyunsaturated fat consumption, which was restricted to the small subset of men with a family history of prostate cancer (41). Nevertheless, our findings are generally inconsistent with those in the literature and require replication in studies of screen-detected cancer.

The most significant weakness in this study was the use of FFQs to measure nutrient intake. Recently, some investigators have questioned the validity of FFQs for dietary assessment (46, 47), and some scientists have challenged their continued use in epidemiologic research (48, 49), although this view is controversial. As demonstrated in studies of dietary fat and breast cancer risk (50, 51), there is a distinct possibility that moderate or weak associations of diet with cancer risk cannot be detected using FFQs but can be detected using multiple-day food records. We believe that strong associations will probably be detected across extreme intake categories, and our concern is that weak but meaningful associations may not be detected. We also chose not to follow several common practices used in nutritional epidemiology. First, we did not adjust model results for multiple dietary factors simultaneously, because most dietary covariates are highly correlated and poorly measured, and their use could therefore lead to unstable models with unpredictable results (52). Second, we did not conduct multiple subgroup analyses—for example, examining results stratified by age or nutrients stratified by type of dietary exposure (e.g., folate from food vs. folate from supplements)—because, lacking a strong biologic rationale, this increases the likelihood of chance findings. It is possible that true, subgroup-specific or nutrient-adjusted associations were missed in our analyses. Our plan is to examine these more complex hypotheses in future analyses based on biomarkers of diet and then attempt to confirm the results using dietary intake data.

There are unique aspects of this study that both increase its quality and limit its generalizability. The most significant are that study participants had PSA levels less than 3 ng/mL at study entry, there was annual screening (PSA plus DRE) during the 7 years of the trial, and determination of the presence or absence of disease was based on endpoint biopsies. Thus, almost all of the cancers that were detected were local-stage, and while the use of endpoint biopsies to identify cancer cases and noncases minimized detection bias, it also identified cancers that would never have been detected by means of either screening or clinical symptoms. A second unique aspect of this study is the use of uniformly graded Gleason scores of 8–10 to define high-grade disease, in contrast to other studies that have used a mix of stage (often surgical and clinical) and grade, as well as long-term clinical outcomes, to define "aggressive" disease. Taken together, the mix of cancer phenotypes in the PCPT may differ markedly from the phenotype mixes in studies that are based on cancers detected by screening alone or by locally defined standards of clinical practice. Thus, risk factors for cancers identified in the PCPT could be quite different from those for clinically detected or advanced-stage disease. Nevertheless, a major strength of this study is the mitigation of the detection biases present in most observational cohort studies in which PSA levels and DREs affect the decision to perform a prostate biopsy. Use of PSA screening is probably associated with dietary patterns (53), such that biases due to screening may have seriously confounded the results of previous studies.

Table 4. Associations of Daily Dietary and Total Micronutrient Intake With the Risks of Low- and High-Grade Prostate Cancer, Prostate Cancer Prevention Trial, 1994–2003

	Quartile of Dietary or Macronutrient Intake[a]				*P* for Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Vitamin C, mg					
Diet	<78.7	78.7–122.6	122.7–179.1	>179.1	
OR (95% CI) for GS 2–7	1.00 (referent)	1.09 (0.93, 1.28)	1.05 (0.89, 1.23)	1.05 (0.89, 1.25)	0.701
No. of cases/total	359/2,277	417/2,428	402/2,387	398/2,340	
OR (95% CI) for GS 8–10	1.00 (referent)	1.29 (0.79, 2.12)	0.97 (0.57, 1.67)	1.24 (0.71, 2.15)	0.717
No. of cases/total	30/1,948	38/2,049	27/2,012	32/1,974	
Total	<120.1	120.1–217.6	217.7–636.4	>636.4	
OR (95% CI) for GS 2–7	1.00 (referent)	1.02 (0.88, 1.19)	0.94 (0.80, 1.10)	1.03 (0.88, 1.21)	0.965
No. of cases/total	399/2,414	418/2,442	385/2,383	374/2,193	
OR (95% CI) for GS 8–10	1.00 (referent)	1.29 (0.79, 2.09)	0.87 (0.51, 1.49)	1.24 (0.75, 2.06)	0.750
No. of cases/total	32/2,047	38/2,062	25/2,023	32/1,851	
Zinc, mg					
Diet	<9.6	9.6–13.1	13.2–17.7	>17.7	
OR (95% CI) for GS 2–7	1.00 (referent)	1.05 (0.89, 1.24)	0.98 (0.81, 1.19)	1.13 (0.89, 1.44)	0.518
No. of cases/total	368/2,230	404/2,386	384/2,426	420/2,390	
OR (95% CI) for GS 8–10	1.00 (referent)	0.90 (0.55, 1.48)	0.54 (0.29, 1.02)	0.62 (0.28, 1.38)	0.113
No. of cases/total	41/1,903	37/2,019	23/2,065	26/1,996	
Total	<13.1	13.1–21.7	21.8–31.2	>31.2	
OR (95% CI) for GS 2–7	1.00 (referent)	1.05 (0.89, 1.24)	0.99 (0.84, 1.16)	1.12 (0.94, 1.33)	0.323
No. of cases/total	379/2,337	410/2,437	381/2,374	406/2,284	
OR (95% CI) for GS 8–10	1.00 (referent)	0.87 (0.52, 1.46)	0.92 (0.56, 1.52)	0.90 (0.52, 1.54)	0.772
No. of cases/total	39/1,997	29/2,056	31/2,024	28/1,906	
Carotenoids (excluding lycopene), μg					
Diet	<5,342	5,342–8,340	8,341–12,799	>12,799	
OR (95% CI) for GS 2–7	1.00 (referent)	1.12 (0.96, 1.31)	0.95 (0.81, 1.12)	1.00 (0.84, 1.18)	0.504
No. of cases/total	373/2,319	430/2,392	379/2,382	394/2,339	
OR (95% CI) for GS 8–10	1.00 (referent)	0.85 (0.52, 1.38)	0.70 (0.41, 1.17)	0.82 (0.49, 1.40)	0.353
No. of cases/total	38/1,984	32/1,994	27/2,030	30/1,975	
Total	<7,500	7,500–12,499	12,500–23,450	>23,450	
OR (95% CI) for GS 2–7	1.00 (referent)	0.88 (0.75, 1.04)	0.94 (0.80, 1.09)	0.98 (0.83, 1.15)	0.996
No. of cases/total	383/2,236	341/2,182	453/2,700	399/2,314	
OR (95% CI) for GS 8–10	1.00 (referent)	1.22 (0.74, 2.04)	0.92 (0.54, 1.56)	1.28 (0.77, 2.13)	0.572
No. of cases/total	29/1,882	33/1,874	30/2,277	35/1,950	
Dietary lycopene, μg	<3,999	3,999–6,646	6,647–10,918	>10,918	
OR (95% CI) for GS 2–7	1.00 (referent)	1.13 (0.97, 1.32)	1.00 (0.85, 1.18)	1.06 (0.89, 1.26)	0.897
No. of cases/total	380/2,342	419/2,364	388/2,411	389/2,315	
OR (95% CI) for GS 8–10	1.00 (referent)	1.22 (0.73, 2.04)	1.50 (0.90, 2.51)	1.33 (0.76, 2.34)	0.221
No. of cases/total	30/1,992	31/1,976	37/2,060	29/1,955	
Calcium, mg	<598	598–841	842–1,165	>1,165	
Diet					
OR (95% CI) for GS 2–7	1.00 (referent)	1.19 (1.01, 1.41)	1.01 (0.84, 1.21)	1.27 (1.02, 1.57)	0.165
No. of cases/total	346/2,210	420/2,367	368/2,414	442/2,441	

Table continues

In conclusion, in this unique sample of local-stage, biopsy-detected cancers, we found no evidence that dietary or supplemental intake of nutrients often proposed to prevent prostate cancer, including lycopene, n-3 fatty acids, vitamin D, vitamin E, and selenium, was associated with risk of low- or high-grade cancer. Our finding that

Table 4. Continued

	Quartile of Dietary or Macronutrient Intake[a]				P for Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
OR (95% CI) for GS 8–10	1.00 (referent)	0.48 (0.29, 0.82)	0.57 (0.33, 1.00)	0.43 (0.21, 0.89)	0.034
No. of cases/total	48/1,912	24/1,971	31/2,077	24/2,023	
Total	<689	689–972	973–1,357	>1,357	
OR (95% CI) for GS 2–7	1.00 (referent)	1.06 (0.90, 1.25)	0.95 (0.80, 1.14)	1.17 (0.97, 1.42)	0.222
No. of cases/total	366/2,250	403/2,389	366/2,384	441/2,409	
OR (95% CI) for GS 8–10	1.00 (referent)	0.51 (0.30, 0.86)	0.69 (0.41, 1.18)	0.46 (0.24, 0.89)	0.053
No. of cases/total	47/1,931	24/2,010	34/2,052	22/1,990	
Vitamin D, μg					
Diet	<3.1	3.1–4.5	4.6–6.7	>6.7	
OR (95% CI) for GS 2–7	1.00 (referent)	1.02 (0.87, 1.20)	1.07 (0.91, 1.27)	1.10 (0.91, 1.33)	0.261
No. of cases/total	360/2,258	390/2,388	409/2,399	417/2,387	
OR (95% CI) for GS 8–10	1.00 (referent)	0.84 (0.52, 1.36)	0.70 (0.41, 1.21)	0.82 (0.45, 1.49)	0.402
No. of cases/total	39/1,937	33/2,031	26/2,016	29/1,999	
Total	<4.2	4.2–8.1	8.2–14.6	>14.6	
OR (95% CI) for GS 2–7	1.00 (referent)	1.04 (0.88, 1.22)	1.02 (0.87, 1.19)	1.14 (0.97, 1.35)	0.142
No. of cases/total	369/2,323	397/2,401	388/2,369	422/2,339	
OR (95% CI) for GS 8–10	1.00 (referent)	0.83 (0.49, 1.39)	1.06 (0.66, 1.72)	0.82 (0.48, 1.41)	0.757
No. of cases/total	37/1,991	28/2,032	36/2,017	26/1,943	
Docosahexaenoic acid + eicosapentaenoic acid, mg					
Diet	<0.06	0.06–0.12	0.13–0.24	>0.24	
OR (95% CI) for GS 2–7	1.00 (referent)	1.09 (0.93, 1.27)	1.05 (0.90, 1.23)	1.08 (0.92, 1.28)	0.456
No. of cases/total	378/2,372	404/2,348	399/2,408	395/2,304	
OR (95% CI) for GS 8–10	1.00 (referent)	1.25 (0.75, 2.09)	1.20 (0.71, 2.03)	1.52 (0.89, 2.58)	0.163
No. of cases/total	28/2,022	33/1,977	31/2,040	35/1,944	
Total	<0.07	0.07–0.14	0.15–0.28	>0.28	
OR (95% CI) for GS 2–7	1.00 (referent)	1.05 (0.90, 1.23)	1.05 (0.90, 1.24)	1.11 (0.94, 1.31)	0.230
No. of cases/total	379/2,377	400/2,381	401/2,425	396/2,249	
OR (95% CI) for GS 8–10	1.00 (referent)	1.31 (0.78, 2.20)	1.30 (0.77, 2.20)	1.46 (0.86, 2.50)	0.193
No. of cases/total	27/2,025	34/2,015	33/2,057	33/1,886	
Folate, μg of α-tocopherol equivalents					
Diet	<458	458–614	615–809	>809	
OR (95% CI) for GS 2–7	1.00 (referent)	1.07 (0.91, 1.27)	1.00 (0.83, 1.19)	0.94 (0.75, 1.16)	0.428
No. of cases/total	367/2,260	409/2,341	408/2,423	392/2,408	
OR (95% CI) for GS 8–10	1.00 (referent)	0.96 (0.59, 1.59)	0.80 (0.45, 1.43)	0.82 (0.41, 1.66)	0.480
No. of cases/total	38/1,931	34/1,966	28/2,043	27/2,043	
Total	<582	582–1,023	1,024–5,291	>5,291	
OR (95% CI) for GS 2–7	1.00 (referent)	0.97 (0.82, 1.15)	1.11 (0.94, 1.30)	1.04 (0.88, 1.23)	0.306
No. of cases/total	372/2,298	390/2,437	413/2,322	401/2,375	
OR (95% CI) for GS 8–10	1.00 (referent)	1.09 (0.64, 1.84)	1.07 (0.66, 1.76)	0.90 (0.51, 1.56)	0.714
No. of cases/total	35/1,961	33/2,080	33/1,942	26/2,000	

Abbreviations: CI, confidence interval; GS, Gleason score; OR, odds ratio.

polyunsaturated fat was associated with increased risk of high-grade prostate cancer suggests that further research into inflammation and other metabolic processes affected by these fats may be important in understanding prostate cancer etiology. Our finding of a positive association of calcium with low-grade disease and an inverse association with high-grade disease adds to the inconsistency of findings related to calcium, which may be important and may require further inquiry. The consistent and strong findings from ecologic studies that the adoption of a diet high in fat and animal products, characteristic of Western diets (54–56), increases prostate cancer risk are perplexing. It is possible that these ecologic studies are yielding results that do not reflect individual-level cancer risk, that the specific aspects of diet affecting prostate cancer risk have not been adequately measured or identified, or that the association of a Western-style diet with prostate cancer risk cannot be reduced to studies of a single nutrient or set of nutrients.

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