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Original Contribution

Calcium, Vitamin D, and Dairy Product Intake and Prostate Cancer Risk

The Multiethnic Cohort Study

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High intakes of calcium and dairy products have been suggested to be related to prostate cancer risk. Such associations were examined in the Multiethnic Cohort Study (1993–2002) among 82,483 men who completed a detailed quantitative food frequency questionnaire. During a mean follow-up of 8 years, 4,404 total cases of prostate cancer were identified. In Cox proportional hazards models, no association was found between calcium and vitamin D intake and total, advanced, or high-grade prostate cancer risk, whether for total intake, intake from foods, or intake from supplements, among all male participants or among nonusers of supplemental calcium. No association of calcium or vitamin D intake was seen across racial/ethnic groups. In analyses of food groups, dairy product and total milk consumption were not associated with prostate cancer risk. However, low-/nonfat milk was related to an increased risk and whole milk to a decreased risk of total prostate cancer; after stratification, these effects were limited to localized or low-grade tumors. Although the findings from this study do not support an association between the intakes of calcium and vitamin D and prostate cancer risk, they do suggest that an association with milk consumption may vary by fat content, particularly for early forms of this cancer.

calcium; cohort studies; dairy products; ethnic groups; prostatic neoplasms; vitamin D

Abbreviations: CI, confidence interval; PSA, prostate-specific antigen; QFFQ, quantitative food frequency questionnaire; RR, relative risk.

High intakes of calcium and dairy products have been suggested to play a role in prostate cancer development via vitamin D metabolism (1–3). A hypothesized mechanism is that high calcium consumption lowers the level of circulating 1,25-dihydroxyvitamin D, an inhibitor of prostate carcinogenesis (2). Indeed, a recent meta-analysis of prospective studies reported that high calcium intake was related to a 39 percent increase in risk for total prostate cancer and a 46 percent increase in risk for advanced prostate cancer, and that high dairy product intake was associated with an 11 percent increase in total prostate cancer risk and a 33 percent increase in advanced prostate cancer risk (4). These results suggest that high intakes of calcium and dairy products may affect tumor differentiation as well as development. Among individual prospective cohort studies, some studies support the positive associations (5–8), but other investigations are not supportive (9–13). Furthermore, the only randomized controlled clinical trial found no increase in prostate cancer risk with calcium supplementation over a period of 4 years (14).

Studies that investigated individual types of dairy products have suggested that a positive association may be limited to low- or nonfat milk rather than whole milk, cheese, yogurt, or other dairy items (3, 5, 8), but an explanation for

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this specificity is not clear. With the recommendations for daily calcium intake (1,200 mg) and low- or nonfat milk (3 cups/0.71 liter) or equivalent milk product consumption for adults (15, 16), as well as the known health benefits of adequate calcium intake, the role of calcium as a potential risk factor for prostate cancer needs to be clarified. In this analysis, we investigated the intakes of calcium, vitamin D, and dairy products in relation to prostate cancer risk in a large, multiethnic cohort where the incidence of the disease differs greatly by ethnicity.

MATERIALS AND METHODS

Study cohort

The design and implementation of the Multiethnic Cohort Study have been described in detail elsewhere (17). Briefly, more than 215,000 adults aged 45–75 years, including 96,958 men, completed a mailed questionnaire on diet, medical history, and lifestyle at baseline in 1993–1996. Participants are mainly from five racial and ethnic populations living in California and Hawaii: African Americans, Native Hawaiians, Japanese Americans, Latinos (born in the United States, Mexico, or South and Central America), and Whites. For the analyses, we excluded men who did not self-identify as one of the five racial/ethnic groups ($n = 5{,}944$), men with a prior occurrence of prostate cancer either by report on the questionnaire or through tumor registry data ($n = 2{,}890$), men with implausible dietary data based on total energy intake or its components ($n = 3{,}653$) (18), and men with missing or incomplete information on height, weight, educational level, or smoking ($n = 1{,}988$), leaving a total of 82,483 men for the analysis. The baseline questionnaire did not ask about prior prostate-specific antigen (PSA) screening tests. However, in 2000–2002, information on PSA screening utilization was collected from approximately 80 percent of the surviving male participants in the cohort using a brief follow-up (second) questionnaire (19).

Dietary assessment

Dietary intake from foods was assessed by a self-administered quantitative food frequency questionnaire (QFFQ) covering the previous year. The QFFQ, with over 180 items, was developed from 3-day measured food records collected on about 60 men and women of each ethnic group (17). A calibration study was also conducted and showed satisfactory correlations (range: 0.55–0.74) between the QFFQ and three 24-hour recalls for all ethnic and sex groups being studied (20). Correlations for energy-adjusted nutrients were 0.67 for calcium and 0.61 for vitamin D. Nutrient intakes from the QFFQ were calculated by the food composition table that has been developed and maintained at the Cancer Research Center of Hawaii for use in the Multiethnic Cohort Study. In addition to the QFFQ, the baseline questionnaire contained questions about the use of vitamin and mineral supplements, including multivitamin and individual calcium supplements. Subjects were asked to indicate whether the supplements had been used at least weekly during the past year and also were asked to indicate the duration and frequency of use for each supplement. For this analysis, only regular supplement use, defined as use for >1 year, was considered. For calcium supplements, subjects were asked to indicate the approximate dosage per tablet: ≤250 mg, 300–600 mg, 625–1,000 mg, or ≥1,250 mg, if known. Calcium supplement users who did not provide a dosage (24 percent of users) were assigned to the lowest category. No information on the specific multivitamin brand was collected, and the calcium level in a multivitamin was estimated at 181 mg per tablet on the basis of a composite of the levels in the two multivitamin brands most frequently reported in the dietary recalls in the calibration study (Centrum Silver and Centrum Hi Potency; Wyeth Consumer Healthcare, Madison, New Jersey) (21). Vitamin D from multivitamins was similarly estimated to be 400 IU per tablet. Total calcium intake included contributions from foods, individual calcium supplements, and multivitamins. Total vitamin D included intake from foods and multivitamins.

Case identification

Incident cases of prostate cancer were identified by linkage of the cohort to the Surveillance, Epidemiology, and End Results (SEER) cancer registries covering Hawaii and California; case ascertainment was complete through December 31, 2002. The cohort was also linked to the Hawaii and California state death files and to the National Death Index file through December 31, 2002. In this analysis, we considered all prostate cancer cases as events except in situ tumors. Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized), while high-grade prostate cancer was based on a Gleason score of ≥7 (categorized as poorly differentiated). During the average follow-up period of 8 years, a total of 4,404 incident cases were identified; of the cases, 738 were classified as advanced and 823 as high grade.

Statistical analysis

Nutrient and food intakes were divided into quintiles on the basis of the distribution of the intake among all men in the cohort. Nutrient and food intakes were adjusted for total energy intake by use of nutrient density and residual methods (22). The findings were similar; the results based on the residual method are presented so that they can be compared with the results of others. Age- and ethnicity-adjusted averages of dietary and other variables collected at baseline were computed via poststratification (23), weighted to the 5-year age and ethnic group distribution of all male participants. We used Cox proportional hazards models with age as the time metric to calculate relative risks and 95 percent confidence intervals for prostate cancer. The proportionality assumption was tested by Schoenfeld residuals and found to be met. All Cox models were stratified on ethnicity, time since cohort entry (<2 years, 2–5 years, >5 years), body mass index (weight (kg)/height (m)^2: <22.46, 22.46–24.99, 25.00–29.99, ≥30.00), education (eighth grade or less, 9th–12th grade, some college or vocational school, graduated college or higher), family history of prostate cancer (yes

TABLE 1. Baseline characteristics of men according to intake of total calcium, Multiethnic Cohort Study, 1993–2002

	Total calcium intake (mg/day)				
	<470	470–<692	692–<935	935–<1,301	≥1,301
Median age at cohort entry (years)	60	60	61	60	60
Ethnicity (%)*					
African American	22.6	23.3	20.4	17.6	16.2
Native Hawaiian	18.6	22.9	19.7	19.0	19.8
Japanese American	23.7	26.3	22.1	16.9	11.0
Latino	9.5	15.2	19.0	23.8	32.5
White	8.9	17.9	22.7	25.7	24.7
Family history of prostate cancer (%)†	6.2	6.7	6.8	7.2	6.9
Education (years)†	13.1	13.3	13.4	13.4	13.3
Body mass index (kg/m^2)†	26.0	26.0	26.0	26.1	26.2
Current smoking (%)†	21.5	18.3	17.0	16.9	16.7
Regular multivitamin use (%)†,‡	8.6	24.6	36.5	48.1	61.4
Regular calcium supplement use (%)†,‡	0.6	1.8	4.0	9.9	29.5
Daily dietary intake†					
Energy (kcal)	1,408	1,856	2,227	2,645	3,407
Total fat (% of energy)	29.5	30.1	30.2	30.5	30.5
Total vitamin D (IU)	78	175	285	435	679
Phosphorus (mg)	722	1,030	1,299	1,611	2,212
Total meat (g)	94	122	144	168	208
Red meat (g)	32	41	48	55	69
Total dairy products (g)	58	116	180	257	432
Milk (g)	34	77	126	184	314

* Row percentages are shown.
† Values are averages, adjusted for ethnicity and age group by poststratification.
‡ Used at least once a week for more than 1 year.

and no/do not know), and smoking status (never smoker; former smoker; current smoker: <10, 10–19, ≥20 cigarettes/day). Relative risks were also adjusted for energy intake (log-transformed kilocalories/day). We also considered other factors (fat, meat, phosphorus intake, and use of any vitamin or mineral supplement) as covariates but did not include them in the final models because adjustment for these variables did not alter relative risks. The potential adjustment variables were selected because they were associated with prostate cancer risk or prevalence of PSA screening (i.e., smoking status) in our data or because they were reported to be risk factors for prostate cancer in the literature. We tested the linear trends in risk for dietary factors by considering a continuous variable assigned the racial/ethnic-specific median value within the appropriate overall quintile. Analyses were performed separately for less aggressive and more aggressive tumors, on the basis of stage and grade information, to compare with the results of others. We also ran an a priori analysis stratified by ethnicity to examine the consistency across the groups as a measure of robustness of findings. Likelihood ratio tests were performed to assess the interaction between ethnicity and dietary variables related to prostate cancer risk. p values were two sided, and statistical significance was set at $p < 0.05$. All analyses were conducted using SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The mean daily intake among men in the study population, adjusted for age and ethnicity, was 962 mg for total calcium, 833 mg for calcium from foods, 335 IU for total vitamin D, and 148 IU for vitamin D from foods. Overall, 37 percent were regular multivitamin users, and 9 percent reported using individual calcium supplements regularly. Total calcium intake was highest in Latinos (1,158 mg), followed by Whites (1,042 mg), Native Hawaiians (982 mg), African Americans (856 mg), and Japanese Americans (785 mg). Baseline characteristics of the men in the study population by total calcium intake are shown in table 1. Compared with men who had lower intakes, men with higher total calcium intakes tended to be nonsmokers, to use multivitamin or calcium supplements regularly, and to have a diet higher in total calories, total vitamin D, phosphorus, meat, and dairy product consumption.

No association was found between calcium (table 2) and vitamin D (table 3) intakes and total prostate cancer risk,

TABLE 2. Multivariate relative risk and 95% confidence interval of prostate cancer by daily intake of calcium and extent and grade of disease, Multiethnic Cohort Study, 1993–2002*

	Total			Localized			Advanced†			Low grade			High grade‡		
	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval
Total calcium (mg)															
<470	706	1.00		533	1.00		120	1.00		404	1.00		120	1.00	
470–<692	925	1.03	0.93, 1.15	706	1.05	0.93, 1.19	169	1.09	0.85, 1.41	524	1.07	0.93, 1.24	193	1.26	0.98, 1.62
692–<935	949	1.04	0.93, 1.17	753	1.11	0.98, 1.26	148	0.90	0.68, 1.19	586	1.19	1.03, 1.38	170	1.06	0.81, 1.39
935–<1,301	936	1.05	0.93, 1.18	734	1.10	0.96, 1.26	144	0.87	0.64, 1.17	554	1.13	0.96, 1.33	180	1.15	0.86, 1.53
≥1,301	888	1.04	0.91, 1.20	679	1.10	0.94, 1.29	157	0.91	0.65, 1.28	548	1.16	0.97, 1.40	160	1.06	0.76, 1.48
p_{trend}			0.69			0.36			0.38			0.21			0.72
Calcium from supplements (mg)§															
0	2,698	1.00		2,044	1.00		486	1.00		1,596	1.00		508	1.00	
1–<200	1,072	1.02	0.95, 1.10	862	1.07	0.99, 1.17	161	0.88	0.73, 1.06	641	1.07	0.97, 1.18	201	1.03	0.87, 1.22
≥200	634	0.99	0.90, 1.08	499	1.00	0.90, 1.11	91	0.87	0.69, 1.10	379	1.02	0.91, 1.15	114	0.97	0.79, 1.21
p_{trend}			0.88			0.84			0.18			0.61			0.86
Calcium from foods (mg)§															
<417	737	1.00		566	1.00		118	1.00		418	1.00		133	1.00	
417–<604	934	1.01	0.91, 1.13	721	1.01	0.89, 1.14	160	1.11	0.85, 1.44	534	1.08	0.94, 1.25	185	1.06	0.83, 1.36
604–<809	950	1.02	0.91, 1.14	744	1.04	0.92, 1.19	155	1.01	0.76, 1.35	563	1.16	1.00, 1.36	183	0.99	0.75, 1.29
809–<1,123	909	0.99	0.87, 1.13	707	1.00	0.87, 1.16	150	0.99	0.72, 1.36	553	1.14	0.96, 1.36	162	0.88	0.64, 1.19
≥1,123	874	1.02	0.87, 1.19	667	1.06	0.89, 1.27	155	0.97	0.66, 1.43	548	1.20	0.98, 1.48	160	0.87	0.60, 1.27
p_{trend}			0.92			0.56			0.60			0.15			0.30
Calcium from foods (mg)¶															
<417	492	1.00		369	1.00		84	1.00		273	1.00		87	1.00	
417–<604	559	0.96	0.84, 1.10	407	0.91	0.78, 1.07	111	1.14	0.83, 1.58	328	1.08	0.90, 1.30	104	0.96	0.69, 1.33
604–<809	592	1.03	0.89, 1.20	463	1.07	0.90, 1.27	101	1.02	0.71, 1.45	348	1.19	0.97, 1.45	121	1.11	0.79, 1.57
809–<1,123	525	0.94	0.79, 1.12	392	0.94	0.78, 1.15	104	0.99	0.66, 1.48	323	1.10	0.88, 1.38	93	0.86	0.57, 1.28
≥1,123	503	0.98	0.80, 1.20	392	1.05	0.83, 1.32	82	0.79	0.48, 1.31	309	1.13	0.86, 1.49	97	0.89	0.54, 1.45
p_{trend}			0.80			0.51			0.15			0.63			0.51

* Multivariate relative risks were adjusted for the strata variables time since cohort entry, ethnicity, family history of prostate cancer, education, body mass index, and smoking status and also adjusted for energy intake as a covariate. Three models are represented in this table: one using all men for total calcium, one using all men for calcium from supplements and from foods entered together, and one using non-supplement users for calcium from foods.

† Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized).

‡ High-grade prostate cancer was based on a Gleason score of ≥7, categorized as poorly differentiated.

§ Results for intakes from foods and supplements were adjusted for each other.

¶ Includes only nonusers of multivitamins and calcium supplements containing calcium ($n = 51,110$).

TABLE 3. Multivariate relative risk and 95% confidence interval of prostate cancer by daily intake of vitamin D and extent and grade of disease, Multiethnic Cohort Study, 1993–2002*

	Total			Localized			Advanced†			Low grade			High grade‡		
	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval
Total vitamin D (IU)															
<66	639	1.00		467	1.00		123	1.00		377	1.00		126	1.00	
66–<136	938	1.15	1.03, 1.28	701	1.17	1.03, 1.32	179	1.18	0.92, 1.51	544	1.18	1.03, 1.36	183	1.13	0.89, 1.44
136–<256	910	1.06	0.95, 1.19	714	1.13	0.99, 1.28	142	0.88	0.68, 1.15	565	1.18	1.02, 1.36	155	0.89	0.69, 1.15
256–<521	940	1.11	1.00, 1.24	745	1.20	1.06, 1.36	150	0.95	0.73, 1.23	559	1.19	1.03, 1.37	175	1.04	0.81, 1.33
≥521	977	1.09	0.98, 1.22	778	1.17	1.03, 1.33	144	0.90	0.69, 1.18	571	1.16	1.01, 1.35	184	1.04	0.81, 1.35
p_{trend}			0.64			0.13			0.18			0.39			0.75
Vitamin D from supplements (IU)§															
0	2,762	1.00		2,101	1.00		488	1.00		1,640	1.00		516	1.00	
1–400	1,257	1.02	0.95, 1.10	1,003	1.06	0.98, 1.15	193	0.93	0.78, 1.11	740	1.05	0.96, 1.15	240	1.06	0.90, 1.24
>400	385	0.98	0.87, 1.09	301	0.97	0.86, 1.10	57	0.92	0.69, 1.23	236	1.00	0.87, 1.16	67	0.96	0.74, 1.25
p_{trend}			0.88			0.96			0.45			0.74			0.98
Vitamin D from foods (IU)§															
<52	673	1.00		508	1.00		114	1.00		400	1.00		133	1.00	
52–<93	898	1.08	0.97, 1.20	678	1.06	0.94, 1.20	170	1.27	0.98, 1.64	529	1.11	0.97, 1.28	153	0.96	0.75, 1.23
93–<143	972	1.12	1.01, 1.25	764	1.17	1.03, 1.32	157	1.08	0.83, 1.41	566	1.18	1.03, 1.36	210	1.19	0.94, 1.51
143–<215	918	1.03	0.92, 1.15	707	1.04	0.92, 1.19	155	1.05	0.80, 1.38	567	1.16	1.01, 1.35	159	0.87	0.67, 1.13
≥215	943	1.10	0.98, 1.24	748	1.16	1.01, 1.33	142	1.01	0.75, 1.35	554	1.17	1.00, 1.37	168	0.98	0.74, 1.29
p_{trend}			0.39			0.11			0.35			0.14			0.62
Vitamin D from foods (IU)¶															
<52	434	1.00		321	1.00		80	1.00		260	1.00		79	1.00	
52–<93	563	1.09	0.95, 1.25	403	1.03	0.88, 1.21	125	1.46	1.07, 2.00	324	1.12	0.94, 1.34	105	1.11	0.81, 1.52
93–<143	587	1.13	0.99, 1.30	445	1.14	0.98, 1.34	103	1.14	0.82, 1.58	342	1.19	1.00, 1.43	129	1.32	0.97, 1.80
143–<215	550	1.04	0.90, 1.21	429	1.08	0.91, 1.27	92	1.01	0.72, 1.43	347	1.19	0.98, 1.43	93	0.91	0.65, 1.28
≥215	537	1.13	0.96, 1.32	425	1.16	0.97, 1.39	82	1.05	0.72, 1.54	308	1.16	0.95, 1.43	96	1.05	0.73, 1.51
p_{trend}			0.40			0.14			0.31			0.31			0.67

* Multivariate relative risks were adjusted for the strata variables time since cohort entry, ethnicity, family history of prostate cancer, education, body mass index, and smoking status and also adjusted for energy intake as a covariate. Three models are represented in this table: one using all men for total vitamin D, one using all men for vitamin D from supplements and from foods entered together, and one using non-supplement users for vitamin D from foods.

† Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized).

‡ High-grade prostate cancer was based on a Gleason score of ≥7, categorized as poorly differentiated.

§ Results for intake from foods and supplements were adjusted for each other.

¶ Includes only nonusers of multivitamins and calcium supplements containing calcium ($n = 51{,}110$).

TABLE 4. Multivariate relative risk and 95% confidence interval of prostate cancer by daily intake of dairy products and extent and grade of disease, Multiethnic Cohort Study, 1993–2002*

	Total			Localized			Advanced†			Low grade			High grade‡		
	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval
Dairy products (g)															
<49	652	1.00		510	1.00		101	1.00		344	1.00		121	1.00	
49–<113	855	1.00	0.90, 1.11	650	0.98	0.87, 1.11	158	1.16	0.89, 1.52	506	1.06	0.92, 1.22	166	1.04	0.81, 1.34
113–<202	982	1.10	0.99, 1.22	753	1.10	0.97, 1.24	170	1.15	0.88, 1.51	581	1.19	1.03, 1.38	187	1.05	0.82, 1.35
202–<332	988	1.05	0.94, 1.17	767	1.06	0.93, 1.20	163	1.09	0.83, 1.43	604	1.17	1.01, 1.36	178	0.93	0.72, 1.20
≥332	927	1.03	0.92, 1.16	725	1.06	0.93, 1.22	146	0.97	0.72, 1.31	581	1.14	0.97, 1.34	171	0.96	0.73, 1.27
p_{trend}			0.78			0.35			0.27			0.23			0.48
Total milk (g)															
<17	633	1.00		499	1.00		99	1.00		335	1.00		121	1.00	
17–<54	865	1.02	0.92, 1.14	658	0.99	0.87, 1.11	153	1.14	0.88, 1.49	503	1.03	0.89, 1.20	165	1.04	0.81, 1.33
54–<130	949	1.08	0.98, 1.21	718	1.05	0.93, 1.19	175	1.26	0.97, 1.64	562	1.15	0.99, 1.32	186	1.04	0.81, 1.33
130–<256	999	1.07	0.96, 1.19	774	1.06	0.94, 1.19	165	1.15	0.88, 1.50	617	1.19	1.03, 1.38	177	0.94	0.74, 1.21
≥256	958	1.07	0.95, 1.19	756	1.09	0.96, 1.24	146	1.01	0.76, 1.34	599	1.15	0.99, 1.34	174	0.97	0.75, 1.27
p_{trend}			0.40			0.13			0.41			0.07			0.52
Low-/nonfat milk (g)															
0	1,506	1.00		1,119	1.00		283	1.00		873	1.00		318	1.00	
1–<35	681	1.10	1.00, 1.21	530	1.14	1.02, 1.27	116	1.01	0.80, 1.27	408	1.13	1.00, 1.28	118	0.94	0.75, 1.17
35–<123	870	1.09	1.00, 1.19	670	1.10	1.00, 1.22	150	1.12	0.90, 1.38	513	1.17	1.05, 1.32	160	0.96	0.79, 1.18
123–<243	852	1.12	1.02, 1.22	677	1.17	1.05, 1.29	127	0.99	0.79, 1.24	516	1.21	1.07, 1.35	156	0.99	0.81, 1.21
≥243	495	1.16	1.04, 1.29	409	1.28	1.13, 1.45	62	0.81	0.61, 1.09	306	1.25	1.08, 1.44	71	0.80	0.61, 1.05
p_{trend}			0.02			<0.001			0.18			0.002			0.21
Whole milk (g)															
0	3,179	1.00		2,504	1.00		504	1.00		1,837	1.00		574	1.00	
1–<17	301	0.93	0.82, 1.06	229	0.92	0.79, 1.06	47	0.85	0.62, 1.17	191	0.96	0.82, 1.12	51	0.82	0.60, 1.12
17–<43	326	0.96	0.85, 1.08	234	0.90	0.78, 1.04	73	1.23	0.95, 1.61	197	0.89	0.76, 1.05	72	1.17	0.90, 1.53
43–<163	284	0.92	0.81, 1.05	206	0.88	0.76, 1.03	54	0.95	0.70, 1.29	188	0.96	0.82, 1.13	57	0.94	0.70, 1.26
≥163	314	0.88	0.77, 1.00	232	0.84	0.73, 0.98	60	0.99	0.74, 1.34	203	0.88	0.75, 1.03	69	1.00	0.76, 1.32
p_{trend}			0.03			0.02			0.96			0.13			0.99
Yogurt (g)															
0	3,159	1.00		2,443	1.00		534	1.00		1,877	1.00		596	1.00	
1–<8	477	1.03	0.93, 1.14	353	0.98	0.88, 1.11	94	1.18	0.94, 1.49	271	1.00	0.87, 1.14	86	1.03	0.82, 1.31
8–<12	154	1.12	0.94, 1.32	128	1.18	0.98, 1.42	21	0.94	0.60, 1.48	100	1.23	0.99, 1.51	26	1.03	0.69, 1.55
12–<40	356	1.05	0.94, 1.18	285	1.08	0.95, 1.23	48	0.86	0.63, 1.17	222	1.12	0.97, 1.30	60	1.03	0.78, 1.36
≥40	258	0.96	0.84, 1.09	196	0.92	0.79, 1.07	41	0.95	0.68, 1.34	146	0.93	0.77, 1.11	55	1.10	0.82, 1.48
p_{trend}			0.57			0.38			0.64			0.54			0.54

Cheese (g)															
0	1,108	1.00		876	1.00		177	1.00		598	1.00		198	1.00	
1–<2	497	1.00	0.89, 1.11	391	1.00	0.88, 1.13	79	1.01	0.77, 1.34	289	1.02	0.88, 1.18	85	1.04	0.80, 1.36
2–<5	926	1.00	0.91, 1.10	712	0.99	0.89, 1.10	160	1.05	0.84, 1.32	564	1.05	0.93, 1.18	172	1.03	0.83, 1.28
5–<14	957	1.08	0.98, 1.19	733	1.06	0.95, 1.18	160	1.11	0.88, 1.41	592	1.11	0.98, 1.26	183	1.18	0.95, 1.48
≥14	916	1.01	0.91, 1.12	693	0.99	0.88, 1.11	162	1.07	0.83, 1.37	573	1.06	0.92, 1.21	185	1.22	0.96, 1.54
p_{trend}			0.89			0.82			0.74			0.70			0.09

* Multivariate relative risks were adjusted for the strata variables time since cohort entry, ethnicity, family history of prostate cancer, education, body mass index, and smoking status and also adjusted for energy intake as a covariate.

† Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized).

‡ High-grade prostate cancer was based on a Gleason score of ≥7, categorized as poorly differentiated.

whether for total intake, intake from foods only, or intake from supplements, among all male participants or among nonusers of multivitamins or calcium supplements (n = 51,110 participants, including 2,671 cases). Furthermore, there was no evidence for a stronger relation of calcium and vitamin D intake with advanced or high-grade prostate cancer. Dairy product and total milk consumptions were also not associated with total, advanced, or high-grade prostate cancer risk (table 4). However, when low-/nonfat milk and whole milk were investigated separately, a moderate and statistically significant increase in risk of total prostate cancer was seen for low-/nonfat milk (for the highest (≥243 g) vs. the lowest (0 g) quintile: relative risk (RR) = 1.16, 95 percent confidence interval (CI): 1.04, 1.29; $p_{trend} = 0.02$), whereas an inverse association was observed for whole milk (for the highest (≥163 g) vs. the lowest (0 g) quintile: RR = 0.88, 95 percent CI: 0.77, 1.00; $p_{trend} = 0.03$). These findings on low-/nonfat milk and whole milk were related to localized or low-grade prostate cancer but not to advanced or high-grade prostate cancer (for low-/nonfat milk intake of ≥243 g vs. 0 g: RR (localized prostate cancer) = 1.28, 95 percent CI: 1.13, 1.45; $p_{trend} < 0.001$; for whole milk intake of ≥163 g vs. 0 g: RR (localized prostate cancer) = 0.84, 95 percent CI: 0.73, 0.98; $p_{trend} = 0.02$). In order to examine the effect of very high calcium intake on prostate cancer risk, we used a higher cutoff point and still found no association (for ≥2,000 mg vs. 500–<750 mg of calcium: RR (total prostate cancer) = 0.89, 95 percent CI: 0.75, 1.06; RR (advanced prostate cancer) = 0.81, 95 percent CI: 0.54, 1.22) (data not shown).

We also conducted an analysis in which we restricted prostate cancer cases to more aggressive subsets, namely, metastatic and fatal cases. However, no association was seen for these more advanced forms of the disease (data not shown).

In an analysis across four racial/ethnic groups, no association of calcium or vitamin D intake was seen with total prostate cancer risk (table 5). Because of the small number of cases in Native Hawaiians and, therefore, limited statistical power, they were not included in this analysis. The positive association for low-/nonfat milk was significant only in the Latino group. The whole milk finding also appeared to be limited to Latinos. However, the tests of interaction between ethnicity and low-/nonfat or whole milk consumption were nonsignificant ($p_{interaction} = 0.48$ for low-/nonfat milk and 0.53 for whole milk). When the analyses were restricted to localized prostate cancer, the positive association of low-/nonfat milk and the inverse associations of whole milk were seen in Latinos and in Whites (for low/nonfat milk: $p_{trend} = 0.20$ in African Americans, 0.61 in Japanese Americans, 0.002 in Latinos, and 0.05 in Whites; for whole milk: $p_{trend} = 0.26$ in African Americans, 0.26 in Japanese Americans, 0.01 in Latinos, and 0.09 in Whites). The results were similar after excluding cases diagnosed within 2 years of cohort entry (n = 955 cases excluded) (data not shown).

DISCUSSION

In contrast to the results of several recent cohort studies on prostate cancer in the United States (5–8), our results

TABLE 5. Multivariate relative risk and 95% confidence interval of total prostate cancer by daily intakes of calcium, vitamin D, and dairy products and by ethnicity, Multiethnic Cohort Study, 1993–2002*

	African Americans			Japanese Americans			Latinos			Whites		
	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval	Cases (no.)	Relative risk	95% confidence interval
Total calcium (mg)												
<470	273	1.00		204	1.00		105	1.00		86	1.00	
470–<692	268	0.96	0.79, 1.17	290	1.19	0.98, 1.44	149	0.93	0.71, 1.22	171	1.00	0.76, 1.31
692–<935	270	1.10	0.89, 1.35	241	1.12	0.91, 1.37	208	1.01	0.77, 1.32	196	0.87	0.66, 1.15
935–<1,301	206	1.01	0.80, 1.29	202	1.20	0.96, 1.50	260	1.01	0.77, 1.34	245	0.94	0.71, 1.24
≥1,301	169	0.95	0.71, 1.26	125	1.05	0.81, 1.37	318	0.98	0.71, 1.35	226	0.99	0.73, 1.34
p_{trend}			0.76			0.92			0.99			0.82
Total vitamin D (IU)												
<66	224	1.00		144	1.00		159	1.00		84	1.00	
66–<136	281	1.20	0.99, 1.45	245	1.28	1.04, 1.59	201	0.99	0.79, 1.23	169	1.24	0.94, 1.63
136–<256	236	1.06	0.86, 1.30	182	1.07	0.85, 1.35	252	1.13	0.91, 1.40	194	1.04	0.79, 1.37
256–<521	211	0.97	0.79, 1.20	236	1.22	0.98, 1.52	224	1.09	0.87, 1.36	230	1.24	0.95, 1.62
≥521	234	1.12	0.91, 1.38	255	1.23	0.98, 1.53	204	1.00	0.79, 1.26	247	1.09	0.84, 1.42
p_{trend}			1.00			0.25			0.83			0.98
Dairy products (g)												
<49	188	1.00		268	1.00		80	1.00		78	1.00	
49–<113	265	0.97	0.80, 1.19	242	1.02	0.85, 1.22	166	1.09	0.82, 1.45	146	0.91	0.69, 1.21
113–<202	283	1.15	0.94, 1.42	250	1.16	0.97, 1.39	206	1.09	0.82, 1.43	204	0.96	0.73, 1.26
202–<332	252	1.09	0.88, 1.34	190	0.99	0.81, 1.20	282	1.23	0.94, 1.61	233	0.86	0.66, 1.12
≥332	198	0.98	0.77, 1.25	112	1.26	0.99, 1.60	306	1.05	0.79, 1.40	263	0.87	0.66, 1.15
p_{trend}			0.89			0.16			0.91			0.32
Total milk (g)												
<17	154	1.00		252	1.00		94	1.00		101	1.00	
17–<54	282	1.06	0.86, 1.30	236	1.07	0.89, 1.29	157	0.98	0.75, 1.28	155	1.00	0.77, 1.30
54–<130	293	1.26	1.02, 1.56	218	1.06	0.88, 1.28	206	1.00	0.77, 1.29	193	1.02	0.80, 1.31
130–<256	266	1.25	1.00, 1.55	227	1.05	0.87, 1.26	257	1.04	0.81, 1.33	211	0.91	0.71, 1.17
≥256	191	1.06	0.83, 1.34	129	1.20	0.96, 1.51	326	1.03	0.80, 1.32	264	0.98	0.76, 1.25
p_{trend}			0.84			0.22			0.65			0.69
Low-/nonfat milk (g)												
0	486	1.00		361	1.00		355	1.00		244	1.00	
1–<35	187	0.94	0.78, 1.12	189	1.17	0.98, 1.41	138	1.13	0.92, 1.39	133	1.24	1.00, 1.55
35–<123	211	1.19	1.00, 1.41	249	1.05	0.89, 1.24	179	1.17	0.97, 1.42	192	0.98	0.81, 1.20
123–<243	211	1.30	1.09, 1.55	204	1.12	0.94, 1.34	215	1.14	0.95, 1.36	192	0.94	0.77, 1.15
≥243	91	0.92	0.72, 1.17	59	1.09	0.82, 1.45	153	1.32	1.08, 1.62	163	1.19	0.97, 1.47
p_{trend}			0.41			0.45			0.02			0.62
Whole milk (g)												
0	735	1.00		893	1.00		664	1.00		756	1.00	
1–<17	111	1.01	0.82, 1.25	59	0.93	0.71, 1.22	87	1.05	0.83, 1.33	32	0.74	0.51, 1.06

17–<43	142	1.08	0.89, 1.31	45	0.93	0.68, 1.27	79	0.84	0.66, 1.08	40	0.97	0.69, 1.35
43–<163	113	1.07	0.87, 1.33	32	0.81	0.57, 1.17	86	0.85	0.67, 1.08	40	0.90	0.65, 1.26
≥163	85	0.81	0.63, 1.04	33	1.20	0.83, 1.73	124	0.82	0.66, 1.01	56	0.90	0.67, 1.21
p_{trend}			0.15			0.65			0.04			0.48
Yogurt (g)												
0	887	1.00		808	1.00		756	1.00		564	1.00	
1–<8	111	0.98	0.80, 1.21	123	1.05	0.86, 1.27	121	1.11	0.91, 1.35	106	0.97	0.78, 1.20
8–<12	44	1.42	1.02, 1.96	27	0.85	0.57, 1.25	39	1.18	0.85, 1.65	39	1.02	0.73, 1.44
12–<40	94	1.36	1.09, 1.71	66	1.05	0.81, 1.36	71	0.84	0.65, 1.08	108	0.96	0.78, 1.19
≥40	50	0.95	0.70, 1.29	38	1.00	0.71, 1.39	53	0.80	0.60, 1.07	107	0.98	0.79, 1.22
p_{trend}			0.82			1.00			0.08			0.85
Cheese (g)												
0	293	1.00		499	1.00		125	1.00		128	1.00	
1–<2	168	1.06	0.86, 1.29	145	0.86	0.71, 1.04	99	1.37	1.04, 1.81	52	0.87	0.63, 1.21
2–<5	288	1.00	0.84, 1.18	224	0.98	0.83, 1.15	202	1.18	0.94, 1.49	171	0.94	0.74, 1.19
5–<14	260	1.19	1.00, 1.43	126	0.98	0.80, 1.20	284	1.22	0.98, 1.52	254	0.99	0.79, 1.24
≥14	177	1.09	0.89, 1.35	68	0.95	0.73, 1.24	330	1.10	0.88, 1.38	319	0.98	0.78, 1.22
p_{trend}			0.28			0.88			0.50			0.82

* Multivariate relative risks were adjusted for the strata variables time since cohort entry, family history of prostate cancer, education, body mass index, and smoking status and also adjusted for energy intake as a covariate.

from the large Multiethnic Cohort Study do not support the hypothesis that calcium intake is associated with an increased risk of prostate cancer. We also found no association between vitamin D intake and risk. However, we observed a weak positive association of low-/nonfat milk and a weak inverse association of whole milk consumption, which observations were limited to localized prostate cancer. There was also no evidence for a stronger association of calcium, vitamin D, or dairy product intake with the risk of advanced or high-grade prostate cancer. The same patterns were seen across the four larger racial/ethnic groups. Although the effects were not significantly different across ethnic groups, the low-/nonfat and whole milk associations were particularly strong and significant for Latinos.

The Health Professionals Follow-up Study reported a twofold increase in the risk of advanced prostate cancer with high calcium intake but no association for total prostate cancer risk (6). However, no relation was found for dairy food intake and either total or advanced prostate cancer in this (6) or an earlier (12) report. Several other cohort studies also failed to observe statistically significant associations between dairy product or milk consumption and prostate cancer risk (7, 9, 10, 13), as did our study. Because dairy products contain a variety of components in addition to calcium, such as fat, protein, lactose, phosphorus, and added vitamin D, the results of such studies may reflect the effects of any of these constituents. Notably, Baron et al. (14) after 4 years of follow-up found no increase in prostate cancer risk among men randomly assigned in an intervention study to take daily calcium supplementation of 1,200 mg. Although most studies found null results for dietary vitamin D, dietary intake data alone do not permit a firm conclusion, because a major source of vitamin D in the body is endogenous production from solar exposure (8, 10, 24, 25).

We did see a moderately elevated risk associated with low-/nonfat milk consumption and a slightly decreased risk for whole milk. Some other studies have reported a positive association for low- or nonfat milk but not for whole milk (5, 8). No clear explanation for this positive association was given, although a few possible reasons were suggested. Since vitamin D is fat soluble, this vitamin may be less well absorbed from fat-reduced milk, leading to lower vitamin D levels among low-fat milk consumers. However, bioavailability of vitamin D from whole milk and nonfat milk was reported to be similar in one study (26). Fat removal from milk could simultaneously decrease the content of lipid-soluble, potentially cancer-protective components such as vitamin E and beta-carotene (27–29). However, we found no studies to support this conjecture. Insulin-like growth factor 1 in milk has been suggested to increase prostate cancer risk (8, 30), yet the direct association with low-/nonfat milk only that we found would not be explained by this mechanism. Since the positive association of low-/nonfat milk was limited to localized prostate cancer, we speculate that low-/nonfat milk consumption might be a marker of PSA screening utilization as a health-conscious behavior. When we investigated the PSA utilization data from the second questionnaire (19), high intake of low-/nonfat milk was associated with an increase of PSA utilization, whereas whole milk consumption showed an inverse relation. However, other dietary variables not associated with prostate cancer (e.g., calcium and vitamin D) were also positively associated with PSA utilization. Also, the reason for the strongest association between low-/nonfat milk and prostate cancer risk in Latinos is not clear. Latinos born in the United States were more likely to utilize PSA screening than those born in Mexico or South and Central America, yet the association between low-/nonfat milk consumption and PSA utilization was similar in both groups and did not differ from those of other ethnic groups. Clearly, the relation between low-/nonfat milk and prostate cancer risk requires further investigation.

Some cohort studies reporting a positive association between calcium intake and prostate cancer contained a wider range of calcium intake than did others (6, 7). The highest category of intake in these studies (e.g., the Health Professionals Follow-up Study) was $\geq$2,000 mg/day. When we used this higher cutoff point in our study, we still found no association for total or advanced prostate cancer.

Our study had several limitations. As noted above, sources of vitamin D in the body include synthesis in skin from solar ultraviolet B exposure, in addition to foods and supplements. Unfortunately, we did not assess solar exposure at baseline, and biomarkers of vitamin D status, such as serum 25-hydroxyvitamin D or vitamin D receptor gene polymorphism, were not available for this analysis (31). Further, we did not have repeated dietary assessments during the follow-up period for this analysis to reflect possible dietary changes. Although the effects of measurement error in dietary intake could not be removed in our study, a previously conducted calibration study had demonstrated that adjustment for energy intake improved the quality of the assessments (20). We had also demonstrated that our limited set of questions on the use of vitamin and mineral supplements in the baseline questionnaire could quantify nutrient intakes with reasonable accuracy (21). Finally, we were not able to control for reported PSA utilization in the risk models because the second questionnaire was administered close to the end of the follow-up period (December 2002), and the questionnaire was not detailed enough to distinguish PSA tests as a diagnostic tool from those performed for screening purposes. However, because PSA utilization is related to calcium and milk intake, it possibly acted as a confounding factor (19). We did adjust for behaviors such as smoking that were related to screening. It has been proposed that, in the PSA era, only very strict criteria should be used to define aggressive prostate cancer in order to adequately detect risk factors for this cancer (32). However, we still found no associations when we restricted our analyses to either metastatic or fatal prostate cancer.

Strengths of our report include a prospective design minimizing recall bias, a large number of subjects of several ethnic origins, a wide range of dietary intakes, a comprehensive and validated QFFQ, and a capability to control for several confounding factors for prostate cancer.

In conclusion, we found no association between the intakes of calcium and vitamin D and prostate cancer risk, but low-/nonfat milk consumption was moderately associated with higher risk and whole milk consumption was associated with slightly decreased risk of prostate cancer.

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