Calcium, Dairy Products, and Risk of Prostate Cancer in a Prospective Cohort of United States Men

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Abstract

Intake of calcium and/or dairy products has been
associated with increased risk of prostate cancer in
some epidemiological studies. One potential biological
mechanism is that high calcium intake down-regulates
1,25 dihydroxy vitamin D$_3$, which may increase cell
proliferation in the prostate. We examined the association
between calcium, dairy intake, and prostate cancer
incidence in the Cancer Prevention Study II Nutrition
Cohort, a prospective cohort of elderly United States
adults. Participants in the study completed a detailed
questionnaire on diet, medical history, and lifestyle at
enrollment in 1992–1993. After excluding men with a
history of cancer or incomplete dietary information,
65,321 men remained for analysis. During follow-up
through August 31, 1999, we documented 3811 cases of
incident prostate cancer. Multivariate-adjusted rate ratios
(RRs) were calculated using Cox proportional hazards
models. Total calcium intake (from diet and supplements)
was associated with modestly increased risk of prostate
cancer [RR = 1.2, 95% confidence interval (CI) =
1.0–1.6 for ≥2000 *versus* <700 mg/day, *P* trend = 0.02).
High dietary calcium intake (≥2000 *versus* <700 mg/day)
was also associated with increased risk of prostate cancer
(RR = 1.6, 95% CI = 1.1–2.3, *P* trend = 0.10), although
moderate levels of dietary calcium were not associated
with increased risk. Dairy intake was not associated with
prostate cancer risk. The association between prostate
cancer and total calcium intake was strongest for men
who reported not having prostate-specific antigen testing
before 1992 (RR = 1.5, 95% CI = 1.1–2.0, *P* trend <
0.01 for ≥ 2000 mg/day of total calcium; RR = 2.1, 95%
CI = 1.3–3.4 ≥2000 mg/day of dietary calcium, *P*
trend = 0.04). Our results support the hypothesis that
very high calcium intake, above the recommended intake
for men, may modestly increase risk of prostate cancer.

Introduction

Calcium from dietary and/or supplemental sources has been
associated with higher risk of prostate cancer in four (1–4) of
six case-control studies, although a statistically significant trend
was reported in only two (1, 4) of these. One additional case-
control study reported no association (5), and one reported
decreased risk with increasing calcium intake (6). Few prospec-
tive studies have examined this relationship; two reported pos-
itive associations with significant trend (7, 8), one suggested a
positive association, but the trend was not significant (9), and
another found no association (10). Dairy products, the main
source of dietary calcium and dietary vitamin D, were associ-
ated with increased prostate cancer risk in 8 (1, 4, 11–16) of 14
case-control studies (1–4, 11–21) and 5 (7, 10, 22–24) of 9
prospective studies (7, 9, 10, 22–26). The evidence for an
association between dairy products, calcium, and prostate can-
cer has been summarized in a recent review (24).

High calcium intake may increase prostate cancer risk by
down-regulating 1,25 D,[2] the active form of vitamin D. The
1,25 D form has been hypothesized to play an important role in
prostate cancer carcinogenesis through inhibition of tumor
growth and proliferation in metastases (27). 1,25 D production
is tightly regulated not only by serum calcium levels but also by
serum levels of phosphorus, an essential mineral abundant in
dairy products.

On the basis of currently available information, adequate
intake of calcium for men > 50 years is considered to be 1200
mg/day (28). Dairy products are a major source of dietary
calcium in the United States and the Dietary Guidelines for
Americans and Food Guide Pyramid recommend two to three
servings of dairy products daily (29).

The potential that calcium adversely affects prostate can-
cer contrast with its possible beneficial effects on colon cancer
(30) and osteoporosis (31). It is, therefore, important to clarify
the role of dietary calcium and supplemental calcium on pros-
tate cancer risk among older men.

We examined the relationship of prostate cancer incidence
to calcium intake from diet and supplements and consumption
of dairy products in a prospective cohort of elderly men. The
large size of the cohort and substantial percentage of men
reporting using calcium supplements allowed us to examine
this relationship across a wide range of calcium intakes.

Materials and Methods

Study Population. Men in this study were selected from the
86,404 male participants in the CPS-II Nutrition Cohort (here-

[2] The abbreviations used are: 1,25 D, 1,25 dihydroxy vitamin D$_3$; CPS-II, Cancer
Prevention Study II; FFQ, food frequency questionnaire; PSA, prostate-specific
antigen; RR, rate ratio; CI, confidence interval.

after referred to simply as the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,192 United States men and women. The Nutrition Cohort, begun by the American Cancer Society in 1992, is a subgroup of the ~1.2 million participants in the CPS-II, a prospective study of cancer mortality established in 1982 (32). Members of the CPS-II cohort who resided in 21 states with population-based state cancer registries were invited to participate in the Nutrition Cohort, as described in detail elsewhere (33).

Participants were 50–74 years of age at enrollment in 1992 or 1993, when they completed a 10-page confidential, self-administered mailed questionnaire that included demographic, medical, behavioral, environmental, occupational, and dietary factors. A follow-up questionnaire was sent to cohort members from September 1997 through August 1998 and a second one from September 1999 through August 2001 to update information and to ascertain newly diagnosed cancers. For living cohort members, the response rate was close to 91% for both questionnaires.

We excluded from this analysis men who were lost to follow-up from baseline through August 31, 1999 ($n = 4507$), who reported any prevalent cancer (except nonmelanoma skin cancer) at baseline ($n = 8874$), or those whose self-report of prostate cancer could not be confirmed ($n = 509$). Also excluded were men who reported extreme values of daily energy intake (<650 or >4000 kcal/day) or who left 10 or more of the 68 questions (15% of items) on the FFQ blank ($n = 7051$), those with four or more (of seven) dairy food questions blank, and those with uninterpretable responses to calcium or multivitamin questions ($n = 142$). The remaining blank responses to diet questions were assumed to represent nonconsumption. After these exclusions, the analytic cohort consisted of 65,321 men.

Identification of Cases of Prostate Cancer. We included a total of 3811 verified incident cases of fatal and nonfatal prostate cancer that occurred between enrollment in 1992 and 1993 and August 31, 1999. Incident cases of prostate cancer were identified initially through a self-report of cancer on the 1997–1998 or 1999–2000 follow-up questionnaires. Previous pilot work in our cohort revealed that we are able to identify the vast majority of prostate cancer through self-reports (sensitivity = 0.90; Ref. 34). Self-reported prostate cancer cases ($n = 3739$) were verified by medical records ($n = 3045$) or from linkage with state cancer registries ($n = 694$). Prostate cancer cases were also identified if recorded as the underlying cause of death on a death certificate through August 31, 1999, among cohort members who did not report the cancer at enrollment ($n = 72$). Ascertainment of all deaths among cohort members is accomplished through linkage of all cohort members with the National Death Index (35).

For analysis of aggressive prostate cancer, we examined a subgroup of prostate cancer cases stages C2 and D and prostate cancer deaths ($n = 569$). We did not have the statistical power to assess separately the association between calcium intake, dairy product consumption, and metastatic prostate cancer (stage D) because of the small number of metastatic prostate cancer cases ($n = 74$).

Dietary Assessment. Usual dietary intake was assessed using a semi-quantitative 68-item FFQ, modified from the brief "Health Habits and History Questionnaire" developed by Block *et al.* (36). Daily nutrient intake was estimated from the FFQ using the Diet Analysis System version 3.8a (37). The FFQ questionnaire asked about portion size (small, medium, and large) and frequency of intake ranging from never or less than

once/month to 2+ times/day for foods and to 6+ times/day for beverages.

Calcium intake was estimated from dietary intake and vitamin supplement use reported on the FFQ. Dietary calcium is provided as a nutrient value directly from the Diet Analysis System program. The questionnaire asked about frequency of use of calcium containing supplements during the past year (multivitamins and calcium). Information about dose was also collected among participants reporting calcium supplement use. Calcium intake was calculated in mg/day; total calcium estimates include contributions from diet, individual calcium supplements, and multivitamin pills. No information on specific multivitamin brand was collected, and the amount of calcium in multivitamin pills was estimated at 130 mg/pill. Nutrient estimates were adjusted for total energy using the residual method (38).

Dairy product consumption was measured from food intake reported on the FFQ. We converted estimated dairy food intake (whole, low fat, and skim milk, cheese, low fat and regular yogurt, and ice cream) into servings using definitions of serving size from the United States Department of Agriculture's Food Guide Pyramid Servings Database (29). We did not consider butter intake because this is not generally included in the dairy food group and is not a major contributor to calcium intake.

The FFQ was validated in 441 Nutrition Cohort participants using four random 24-h recalls collected over a 1-year period as the comparison measure (39). Energy-adjusted correlations that controlled for day-to-day variation in 24-h recalls were 0.68 for dietary calcium and 0.72 for dairy products (39). Vitamin D values were added to the nutrient database using United States Department of Agriculture sources (40). Total vitamin D (IU/day) included intake from diet and multivitamins (estimated to be 400 IU/pill).

Statistical Analysis. Total and dietary calcium intakes were categorized in five categories of mg/day of calcium (<700, 700–999, 1000–1499, 1500–1999, ≥ 2000). These cutpoints correspond with those in a published analysis of a cohort of men with similar characteristics to the Nutrition Cohort (7) and represent a wide range of calcium intake.

We used Cox proportional hazards modeling to examine the association of dietary factors with prostate cancer incidence while adjusting for other potential risk factors. All Cox models were stratified on single year of age at enrollment and adjusted for race (white, black, other). We tested the linear trends by considering the medians of the categories for calcium or dairy intake as continuous variables.

Potential confounders included in the multivariate model were: education (less than high school, high school graduate, some college, college graduate, graduate school); family history of prostate cancer in a brother and/or father (yes/no); total energy intake (quintiles); and total fat intake (quintiles). We also conducted multivariate analysis, including phosphorus intake (mg/day; <900, 900-<1100, 1100-<1300, 1300-<1500, ≥ 1500) and total vitamin D (IU/day; <150, 150-< 365, 365-<580, 580-<800, ≥ 800). Other factors examined, but not included because they either were not associated with disease or did not confound the relation with disease, included body mass index, smoking, physical activity, and intake of vegetables, red meat, lycopene, and fructose. All relative risks reported in the text were obtained from the multivariate Cox models. We used multiplicative interaction terms to examine whether the association between calcium intake and prostate cancer differed by

Table 1   Demographic characteristics of men according to lowest, medium and highest categories of calcium intake, CPS-II Nutrition Cohort, 1992–1999

Covariate	Calcium intake (mg/day)		
	Lowest intake <700 (n = 23,653) Age-adjusted percentage[a] or means	Third level intake 1000–1499 (n = 14,104) Age-adjusted percentage[a] or means	Highest intake ≥2000 (n = 1330) Age-adjusted percentage[a] or means
Age at enrollment (mean yr)	63.1	64.4	65.6
Family history of prostate cancer[b]			
No	88.5	88.0	88.5
Yes	11.5	12.0	11.5
Education[b]			
Less than high school	9.6	5.8	5.6
High school graduate	21.3	17.0	13.3
Some college	27.0	24.6	26.0
College graduate	20.8	22.9	22.1
Graduate school	21.3	29.7	33.3
Smoking status[b]			
Nonsmokers	28.3	36.6	40.0
Current smokers	11.1	7.1	5.6
Former smokers	60.6	56.3	54.4
Body mass index (mean)	26.5	26.3	25.9
Energy intake (calories) (mean)	1790.0	1833.1	1681.1
Total fat intake (g/day) (mean)	76.3	69.7	54.4
Phosphorus intake (mg/day) (mean)	977.1	1404.8	1801.7
Total vitamin D intake (IU/day) (mean)	168.2	427.5	743.9
Dietary calcium (mg/day) (mean)	527.5	1083.4	1603.9
Supplemental calcium (mg/day) (mean)	17.2	110.8	746.7
Lycopene (mcg/day) (mean)	4532.1	4846.3	4567.8
Red meat intake (servings/day) (mean)	0.80	0.60	0.42

[a] Percentages and means are directly adjusted to the age distribution of the entire study population.
[b] Percentages may not sum to 100 because of missing data.

hypothesized effect modifiers, including phosphorus intake, vitamin D intake, and age.

Stratification by PSA screening is potentially important because PSA screening may increase the pool of indolent prostate cancer that would not have progressed if untreated, thus making it more difficult to identify etiologic risk factors (41). Ideally, analyses would be stratified on whether PSA specifically for screening had been performed during the 1992–1999 follow-up interval. However, it was not possible to reliably distinguish screening from diagnostic PSA. We therefore decided to conduct stratified analyses on use of PSA testing before 1992 with the assumption that the early adopters, those who had PSA screening before 1992, were more likely to have received PSA screening during the follow-up period than those who did not report PSA screening before 1992. Information on PSA testing was obtained from the 1997 follow-up questionnaire (the first questionnaire to ask about PSA testing in this cohort), which asked participants when they had first received a PSA blood test and included the response category "before 1992."

Results

Approximately 37% (n = 23,653) of men in the study population reported low total (dietary plus supplement) calcium intake (<700 mg/day) and 2% (n = 1330) reported high total calcium intake (≥ 2000 mg/day). Overall, 33% were multivitamin users, and 8% were using individual calcium supplements.

Milk, mainly low fat and skim milk, was the major source of dietary calcium, accounting for 70% of dietary calcium intake. Milk was also the major dietary source of vitamin D. The correlation between total calcium intake and total vitamin D and phosphorus was 0.57 and 0.77, respectively. Dietary calcium strongly correlated with phosphorus (0.91) and weakly with total vitamin D (0.42).

The age-adjusted percentage of distribution of certain covariates that potentially affect prostate cancer risk varied with total calcium intake (Table 1). Men with higher total calcium intake were older, more educated, thinner, and more likely to be never smokers. In addition, men with higher calcium intake had diets lower in total calories, fat, and red meat and higher in phosphorus and vitamin D.

High intake of total calcium was associated with a small increase in risk of overall prostate cancer (multivariate adjusted RR = 1.2, 95% CI = 1.0–1.6 for ≥2000 *versus* <700 mg/day; Table 2). Importantly, the trend of increasing risk with increasing total calcium intake (*P* trend = 0.02) became stronger and statistically significant when adjusting for phosphorus and total vitamin D intake. The association between total calcium and advanced prostate cancer at diagnosis was similar to that presented for total prostate cancer, although the statistical power to examine very high levels of calcium intake (≥2000 mg/day) was more limited. When results were examined using quintiles of total calcium intake (instead of the absolute categories shown in Table 2), no association between calcium and overall prostate cancer risk was observed (RR = 1.0, 95% CI = 0.9–1.2 for the highest *versus* lowest quintile). However, the highest quintile of calcium intake was associated with increased risk of advanced prostate cancer (RR = 1.3, 95% CI = 0.8–1.9, *P* trend = 0.04).

High dietary calcium intake (≥2000 mg/day) among men not using individual calcium supplements was associated with risk of total and advanced prostate cancer, but no increased risk was seen among men consuming <2000 mg/day, and no sig-

Table 2 Prostate cancer incidence by total calcium intake, CPS-II Nutrition Cohort, 1992–1999

Total calcium intake (mg/day)	Prostate cancer cases	Person-years	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[c]
Total prostate cancer cases					
<700	1323	147,858	1	1	1
700–999	1293	137,184	0.9 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
1000–1499	835	88,023	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
1500–1999	265	23,174	1.2 (1.0–1.3)	1.1 (1.0–1.3)	1.3 (1.1–1.5)
≥2000	95	8,152	1.2 (1.0–1.4)	1.1 (0.9–1.4)	1.2 (1.0–1.6)
			P trend = 0.06	*P* trend = 0.15	*P* trend = 0.02
Advanced prostate cancer cases					
<700	220	140,700	1	1	1
700–999	167	129,905	0.8 (0.6–1.0)	0.8 (0.7–1.0)	0.9 (0.7–1.1)
1000–1499	134	83,505	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.2 (0.9–1.7)
1500–1999	33	21,670	0.9 (0.6–1.3)	0.9 (0.6–1.4)	1.3 (0.8–2.1)
≥2000	15	7631	1.2 (0.7–2.0)	1.2 (0.7–2.1)	1.6 (0.9–3.0)
			P trend = 0.80	*P* trend = 0.66	*P* trend = 0.08

[a] Adjusted for age at entry and race.
[b] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, and education.
[c] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, education, phosphorus and total vitamin D.

Table 3 Prostate cancer incidence by dietary calcium intake CPS-II Nutrition Cohort, 1992–1999[a]

Dietary calcium intake (mg/day)	Prostate cancer cases	Person-years	RR (95% CI)[b]	RR (95% CI)[c]	RR (95% CI)[d]
Total prostate cancer cases					
<700	1454	162,387	1	1	1
700–999	1200	125,682	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
1000–1499	632	67,520	1.0 (0.9–1.1)	1.0 (0.9–1.0)	1.0 (0.9–1.2)
1500–1999	130	12,833	1.0 (0.9–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.5)
≥2000	42	2,832	1.5 (1.1–2.0)	1.4 (1.1–2.0)	1.6 (1.1–2.3)
			P trend = 0.52	*P* trend = 0.76	*P* trend = 0.10
Advanced prostate cancer cases					
<700	247	154,547	1	1	1
700–999	149	118,891	0.8 (0.6–0.9)	0.8 (0.6–0.9)	0.8 (0.6–1.9)
1000–1499	99	64,083	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.1 (0.7–1.7)
1500–1999	19	12,110	0.9 (0.6–1.5)	0.9 (0.6–1.5)	1.2 (0.6–2.4)
≥2000	8	2,608	1.8 (0.9–3.6)	1.7 (0.8–3.5)	2.2 (0.9–5.3)
			P trend = 0.95	*P* trend = 0.95	*P* trend = 0.27

[a] Excludes 353 prostate cancer cases and 5079 noncases taking individual calcium supplements.
[b] Adjusted for age at entry and race.
[c] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, and education.
[d] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, education, phosphorus and total vitamin D.

nificant trend with increasing calcium intake was detected (Table 3). We additionally examined the risk by quintiles of dietary calcium. No association was seen with overall prostate cancer (RR = 1.0, 95% CI = 0.9–1.3 for the highest *versus* lowest quintile) nor for advanced prostate cancer case (RR = 1.1, 95% CI = 0.6–1.8). Calcium supplements were weakly associated with risk of prostate cancer in a model controlling for dietary calcium intake (RR = 1.1, 95% CI = 1.0–1.3 for ≥500 mg *versus* no calcium supplementation, *P* = 0.07). No association was seen with advanced prostate cancer at diagnosis.

Phosphorus and total vitamin D were not associated with total prostate cancer incidence in a model including total calcium intake. However, men taking ≥1500 mg/day of phosphorus were at lower risk of advanced prostate cancer as compared with those with <900 mg/day (RR = 0.6, 95% CI = 0.4–0.9, *P* trend = 0.02). The association between total calcium intake and prostate cancer was not significantly (*P* > 0.05) modified by vitamin D, phosphorus, or age.

Dairy product intake was not associated with either total or advanced prostate cancer. Consumption of four or more servings of dairy products a day compared with less than three/week was not associated with risk of total prostate cancer (RR = 1.1; 95% CI = 0.9–1.3) nor with advanced prostate cancer (RR = 0.9, 95% CI = 0.5–1.4; Table 4). No association was seen with milk intake, the main source of calcium in this cohort (data not shown).

A significant trend (*P* trend < 0.01) of increasing overall prostate cancer risk with increasing total calcium intake was seen among men who reported not having PSA screening before 1992 (RR = 1.5; 95% CI = 1.1–2.0 for calcium intake ≥ 2000 *versus* 700 mg/day; Table 5). In contrast, no association was seen among men who reported having PSA before 1992 (RR = 1.0; 95% CI = 0.6–1.6; *P* for homogeneity of trends <0.01). Similar results (not shown in table) were seen for dietary calcium (RR = 2.1; 95% CI = 1.3–3.4, *P* trend = 0.04, for men reporting no PSA before 1992; RR = 1.1, 95% CI = 0.5–2.3 for men having PSA before 1992).

Table 4 Prostate cancer incidence by dairy intake, CPS-II Nutrition Cohort, 1992–1999

Dairy intake (servings)	Prostate cancer cases	Person-years	RR (95% CI)[a]	RR (95% CI)[b]
Total prostate cancer cases				
<3/week	894	98,107	1	1
3–<7/week	953	102,570	1.0 (0.9–1.1)	1.0 (0.9–1.1)
1–<3/day	1554	162,811	1.0 (1.0–1.1)	1.0 (0.9–1.1)
3–<4/day	273	27,739	1.0 (0.9–1.2)	1.0 (0.9–1.2)
4+/day	137	13,166	1.1 (1.0–1.4)	1.1 (0.9–1.3)
			P trend = 0.21	*P* trend = 0.38
Advanced prostate cancer cases				
<3/week	149	93,296	1	1
3–<7/week	129	97,222	0.8 (0.7–1.1)	0.8 (0.7–1.1)
1–<3/day	225	154,226	0.9 (0.7–1.1)	0.9 (0.7–1.1)
3–<4/day	47	26,267	1.1 (0.8–1.5)	1.0 (0.7–1.4)
4+/day	19	12,400	1.0 (0.6–1.5)	0.9 (0.5–1.4)
			P trend = 0.62	*P* trend = 0.95

[a] Adjusted for age at entry and race.
[b] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, and education.

Table 5 Total calcium and prostate cancer risk by PSA test, Nutrition Cohort, 1992–1997

	PSA	
	No PSA before 1992	PSA before 1992
Total calcium		
<700 mg/day		
No. of cases	787	335
Person-years	87,127	27,467
RR (95% CI)[a]	1	1
RR (95% CI)[b]	1	1
700–999 mg/day		
No. of cases	726	374
Person-years	78,767	29,489
RR (95% CI)[a]	1.0 (0.9–1.1)	1.0 (0.9–1.2)
RR (95% CI)[b]	0.9 (0.8–1.1)	0.9 (0.8–1.1)
1000–1499 mg/day		
No. of cases	451	268
Person-years	49,386	20,962
RR (95% CI)[a]	0.9 (0.8–1.1)	1.0 (0.8–1.2)
RR (95% CI)[b]	1.0 (0.8–1.2)	0.9 (0.7–1.2)
1500–1999 mg/day		
No. of cases	154	76
Person-years	12,923	5,723
RR (95% CI)[a]	1.2 (1.0–1.4)	1.0 (0.8–1.3)
RR (95% CI)[b]	1.4 (1.1–1.8)	1.0 (0.7–1.4)
2000+ mg/day		
No. of cases	59	27
Person-years	4,552	1,924
RR (95% CI)[a]	1.3 (1.0–1.7)	1.1 (0.7–1.6)
RR (95% CI)[b]	1.5 (1.1–2.0)	1.0 (0.6–1.6)
P for trend[b,c]	*P* trend < 0.01	*P* trend = 0.93

[a] Adjusted for age at entry, race.
[b] Adjusted for age at entry, race, family history of prostate cancer, total energy, total fat intake, education, phosphorus, total vitamin D.
[c] *P* for homogeneity of trends: *P* < 0.01.

Discussion

In this cohort of middle-aged to elderly, generally health conscious men, very high total and dietary calcium intake were associated with increased risk of prostate cancer. No association was observed, however, between consumption of dairy products, the main source of calcium, and prostate cancer. Total and dietary calcium were not associated with higher prostate cancer rates among men reporting having PSA screening before 1992, suggesting a role of calcium on development of more clinically relevant prostate cancer.

The increased risk of prostate cancer associated with consumption of ≥2000 mg of calcium a day in this cohort should be interpreted cautiously for several reasons. First, only 2% of men in our cohort and <1% of adult United States males (42) consume ≥2000 mg/day calcium. Secondly, most of our risk estimates are imprecise because of small numbers. Thirdly, the increased risk associated with very high total calcium intake only became apparent after adjusting for vitamin D and phosphorus to separate out the potentially adverse effects of calcium from the potentially beneficial effects of vitamin D and phosphorus. Most dietary sources of calcium such as dairy products contain high levels of vitamin D and phosphorus as well as calcium. In our study, consumption of dairy products (mainly milk) was not associated with increased risk of prostate cancer.

The mechanism underlying an association between calcium and prostate cancer may involve the potential role of 1,25 D in prostate cancer carcinogenesis and the assumption that calcium intake can significantly modify 1,25 D serum levels. A role for 1,25 D in prostate cancer is supported by *in vitro* (27, 43–46) and animal studies (27, 47, 48). *In vitro* studies have shown that 1,25 D receptors are expressed in normal and malignant prostate epithelial cells and can inhibit growth of activated prostate cancer cell lines (46). In addition, prostate cancer tumors in rats treated with 1,25 D were significantly smaller and presented smaller numbers of lung metastases (27), suggesting that 1,25 D may inhibit cancer progression. Observational data on vitamin D serum levels and prostate cancer in men, however, have been inconsistent (49–52), possibly in part because of short half-life of 1,25 D.

The relation between dietary calcium and its correlated nutrients on serum calcium and 1,25 D levels is complex. Levels of 1,25 D (main storage form of vitamin D) are regulated through the activity of renal 1-α-hydroxylase, which stimulates conversion of 25 (OH)D to the active form 1,25 D. The production of 1,25 D in the kidney is tightly regulated through the action of parathyroid hormone in response to low serum calcium and phosphorus levels. Phosphorus intake may also regulate 1,25 D production by binding calcium in the intestine, thus decreasing calcium bioavailability and increasing levels of circulating 1,25 D. It is relevant, therefore, that in this and other studies (1, 7, 9), the association between calcium intake and prostate cancer was stronger when phosphorus and vitamin D were included in the multivariate models. Alternatively, prostate cancer cell growth may also be inhibited through intraprostatic conversion of 25-OH-D_3 to 1,25 D, suggesting an alternative pathway for a role of vitamin D on prostate cancer cell inhibition, which may not involve serum calcium (53).

Data from prospective studies on the association between calcium and prostate cancer are inconsistent. Calcium intake from dairy sources (8) and total calcium intake (dietary and calcium supplements; Ref. 7) were associated with increased risk of prostate cancer in the two prospective studies conducted in the United States. Calcium intake, however, was not associated with prostate cancer risk in two other prospective studies in the Netherlands (10) and in Finland (9). The latter two studies did not include calcium from supplements.

In our CPS-II Nutrition Cohort, the association between high calcium intake and prostate cancer does not appear to be as strong as reported in previous prospective studies. In the Health Professionals Study (7), calcium intake (≥2000 mg/day)

was strongly associated with prostate cancer risk, with RRs of 1.71, 2.97, and 4.57 for total, advanced, and metastatic prostate cancer. In addition, risk of prostate cancer was independently associated with both dietary and supplemental calcium and with milk intake. In the Physicians Health Study (8), intake of >600 mg/day of calcium from dairy products was associated with a slight overall increase in risk of total prostate cancer; stage-specific results were not presented. These differences can be because the advanced cancers comprised a much smaller proportion of the total prostate cancer cases in our cohort than in the two earlier ones, where follow-up was mostly completed before PSA screening was widely implemented. For example, advanced cancers comprised only 14% of total prostate cancers in our cohort, compared with 31% of total prostate cancers in the Health Professionals Study (7). However, even for advanced cancers, our risk estimates were considerable lower than those observed in the Health Professionals Study (7).

A second possibility for the weaker association observed in our study is that calcium intake may be associated more strongly with prostate cancers detected through follow-up of clinical symptoms than with prostate cancers detected through PSA screening. In a cohort with high prevalence of PSA screening, aggressive prostate cancer may be diagnosed at earlier stage than without PSA screening, and stratification by stage at diagnosis may not accurately identify more aggressive cases (41). In addition, tumors diagnosed by PSA screening may be more likely to be smaller or less aggressive than those at the same stage that have progressed naturally (54). This possibility is supported by the fact that calcium intake was more strongly associated with increased risk among men who were the least likely to have received PSA screening during the follow-up period (those who had not already begun PSA testing before 1992). A stronger association between calcium intake and symptomatic prostate cancers (rather than asymptomatic cancers detected through PSA screening) is also consistent with the hypothesized effect of vitamin D on progression of prostate cancer (27).

We did not find an association between dairy intake (main source of calcium) or milk alone and overall or advanced prostate cancer risk in this cohort. An association between dairy products and prostate cancer would be expected because milk (the principal contributor to dairy foods) contains compounds such as calcium and insulin-like growth factors (55), both associated with higher risk of prostate cancer (56). One possible explanation for the lack of association between dairy products and prostate cancer seen in this study is that milk contains compounds that may decrease prostate cancer risk (such as phosphorus and vitamin D), as well as others that may increase risk. Alternatively, poor measurement of dairy intake would be a possible explanation for this lack of association, although the mean intake of dairy products (±SD) in this cohort was (1.2 ± 1.1 serving/day), similar to the national average of 1.3 servings/day in men > age 50 years. The range of dietary calcium was also similar to that reported in previous studies (7, 8).

Strengths of this study are its prospective design, the detailed questionnaire information on amount and frequency of common dairy products, calcium supplement use and dose, and the large number of men included in the study. However, although the number of total prostate cancer cases included in the analysis was large, statistical power to examine associations with more advanced or metastatic prostate cancer was limited.

In summary, results from this and other studies support a role of calcium in prostate carcinogenesis. Because calcium consumption is recommended to prevent osteoporosis and may also decrease risk of colon cancer, future research should try to determine an optimal dose of calcium intake for men and study the impact of PSA on natural history of prostate cancer related to calcium intake.

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Calcium, Dairy Products, and Risk of Prostate Cancer in a Prospective Cohort of United States Men

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